The American Journal of

DIGESTIVE DISEASES

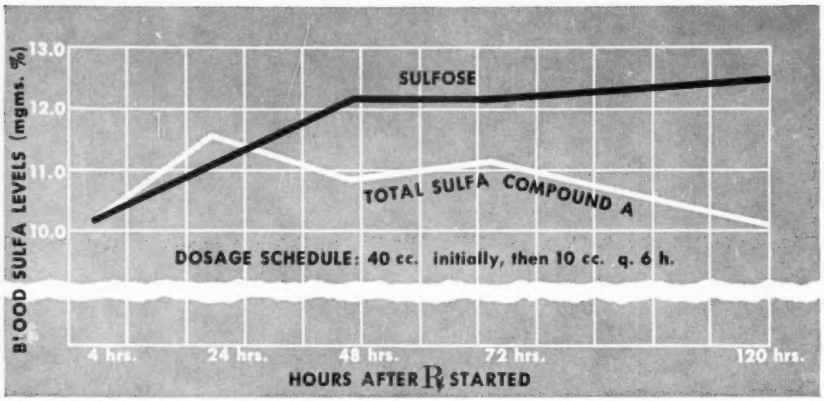
An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

Volume 18 January, 1951 Number 1

A New and Better Triple Sulfonamide Suspension that provides higher, sustained blood levels



A comparison of blood sulfonamide levels on equal doses of SULFOSE and a control preparation having the same sulfonamide composition.

SULFOSE contains sulfadiazine, sulfamerazine and sulfamethazine suspended in a unique, flavored vehicle containing a special alumina gel.

- Unusually palatable
- Stabilized suspension—won't separate
- Easy to measure—pours freely

Each teaspoonful (5 cc.) contains 0.5 Gm. total sulfonamides—0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

SUPPLIED in bottles of 1 pint.

SULFOSE®

TRIPLE SULFONAMIDE SUSPENSION

Wyeth®

WYETH Incorporated, Philadelphia, Pa.

THE OLDEST PERIODICAL IN ITS SPECIAL FIELD ON THE WESTERN HEMISPHERE

Printing Office:
117 E. Main St.
Berne, Indiana

Business and Editorial Office:
425 Lincoln Bank Tower
Fort Wayne 2, Indiana

Advertising Office:
Vining & Meyers
35 East Wacker Drive
Chicago 1, Illinois

Annual Subscription Rate $6.00; Two Years, $10.00

Single Copies: Current Year 80c. Back Years $1.00.

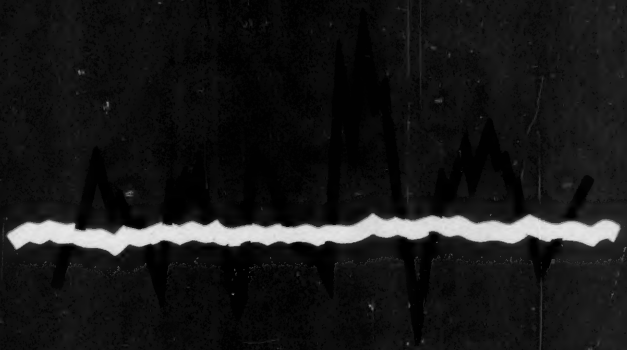
Editor: Beaumont S. Cornell
Fort Wayne, Indiana

Foreign Subscriptions $7.00; two years $12.00

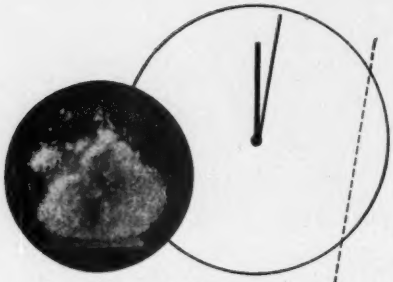
Regional Editor: Franz J. Lust
17 E. 89th St., New York, N. Y.

Published Monthly at 117 East Main St., Berne, Ind.

Correspondence regarding advertising must be addressed to Vining and Myers, 35 E. Wacker Drive, Chicago. Advertising plates must be sent to C. H. Sprunger, 117 E. Main St., Berne Indiana. Subscriptions, reprint orders, etc., may be addressed to 117 E. Main St., Berne Ind., or to 425 Lincoln Bank Tower, Fort Wayne 2, Ind. Manuscripts and books for review must be addressed to Beaumont S. Cornell, 425 Lincoln Bank Tower, Fort Wayne 2, Ind. Illustrations in excess of six per article are charged at cost to the author. Contents of Journal are fully copyrighted. Copyright 1950, by Sandfield Publishing Co., 425 Lincoln Bank Tower, Fort Wayne, Ind., in the U.S.A., Vol. 18, No. 1, January, 1951. Entered as second class matter, Sept. 6, 1950, at the Post Office at Berne, Indiana, under the Act of March 3, 1879.



Donnatal®



a 30 second experiment

Drop a Syntrogel tablet in water. In less than 30 seconds you will note that it "fluffs up" to many times its size. This speedy disintegration increases the adsorptive surface approximately 10,000 times. Syntrogel goes to work in the stomach with equal speed. It adsorbs and neutralizes stomach acid, alleviates heartburn and provides prompt, yet long-lasting relief in most cases. Syntrogel gives symptomatic relief in peptic ulcer, dietary indiscretions and other conditions of gastric hyperacidity.

HOFFMANN-LA ROCHE INC • NUTLEY 10 • N. J.

Syntrogel®

Each Syntrogel tablet contains aluminum hydroxide, calcium carbonate, magnesium peroxide and Syntropan®.

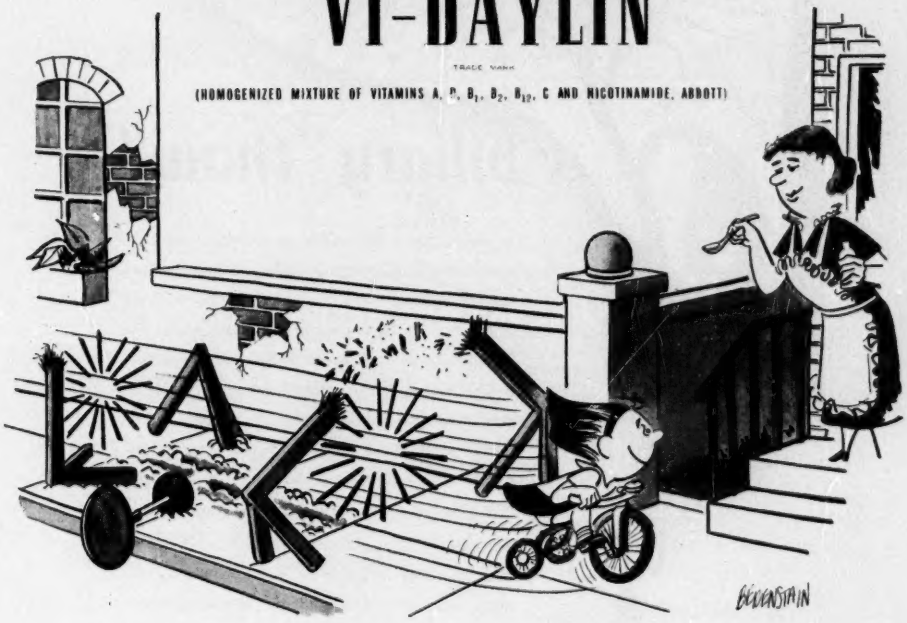
'Roche'

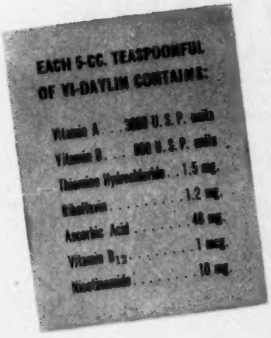
she's heard the call for

VI-DAYLIN

TRADE MARK

(HOMOGENIZED MIXTURE OF VITAMINS A, D, B_1, B_2, B_{12}, C AND NICOTINAMIDE, ABBOTT)





You can cement vitamin-time relations between mother and child by prescribing VI-DAYLIN, a liquid multivitamin treat as eye-appealing as yellow honey, as taste-tempting as lemon candy. Children like it right out of the spoon—no coaxing here. Sound therapy, too, for VI-DAYLIN now supplies *seven* important vitamins, including vitamin B_{12}. Note the formula at left. And VI-DAYLIN is stable at room temperature, doesn't require valuable refrigerator space. Mixes with milk, fruit juice, cereal for infants. No fishy odor, no resistant stains on clothing. At all pharmacies in 90-cc., 8-fluidounce and 1-pint bottles. Abbott

biliary "thaw"

In noncalculous cholangitis, stasis within the common duct often underlies ascending infection. Inflammation and narrowing of the lumen fosters partial obstruction and accumulation of purulent matter. The dynamic action of *Decholin Sodium* and *Decholin*—hydrocholeresis—overcomes this biliary stasis. Under hepatic pressure copious, watery bile sluices down the biliary ducts like a spring thaw, carrying off pus, debris, mucus and stagnant bile. With drainage thus re-established the systemic response is improved.

Therapy should be initiated with small, progressively increasing doses of *Decholin Sodium* given intravenously, followed by a course with *Decholin* tablets.

Decholin®

brand of dehydrocholic acid

Tablets of 3¼ gr. in bottles of 25, 100, 500, and 1000.

Decholin Sodium® (brand of sodium dehydrocholate) in 20% aqueous solution, ampuls of 3 cc., 5 cc., and 10 cc., boxes of 3 and 20.

DECHOLIN and DECHOLIN SODIUM, trademarks reg. U. S. and Canada.

AMES

AMES COMPANY, INC.
ELKHART, INDIANA

NEW- Chlorophyll therapy for peptic ulcers!

CHLORESIUM POWDER

EFFECTIVE- in a recently reported clinical series*, *complete healing was obtained in 58 out of 79 cases of long-standing peptic ulcers within 2 to 7 weeks*—with new chlorophyll powder!

No special diets were required. No restrictions on smoking, alcoholic beverages or daily activity. Three out of four cases got complete symptomatic relief within one to three days!

Incorporating the same water-soluble chlorophyll derivatives well known to the medical profession in Chloresium Ointment and Chloresium Solution (Plain), Chloresium Powder is a completely nontoxic combination product specifically designed to allow prolonged contact of tissue-stimulating chlorophyll with the ulcer crater. At the same time, it provides the essential buffering and protective action found in the usual ulcer medication.

The "Bonus" Action of Chloresium Powder

1. **Prolonged protective coating** (dehydrated powdered okra).
2. **Prompt antacid action** (alum. hydroxide, magnesium trisilicate)—no alkalosis, no acid rebound, no interference with bowel regularity.

PLUS

3. **Promotion of granulation tissue** (with tissue-stimulating chlorophyll). *Only Chloresium Powder gives this tissue-stimulating "bonus!"*

Chloresium Powder, in this clinical trial, demonstrated its effectiveness to the peptic ulcer patient quickly in the form of complete symptomatic relief. It demonstrated its effectiveness to the physician, under roentgenological examination, in prompt healing of the ulcer crater—usually in 2 to 7 weeks—even in cases which had been resistant to other therapy. (The minimum known history of the ulcers treated was two years.)

The freedom from dietary and other restrictions which Chloresium Powder allows has obvious patient appeal and can greatly simplify the task of insuring patient cooperation.

We invite you to try Chloresium Powder on your most resistant case. Just mail the coupon below for a five-day trial supply.

*Offenkrantz, W. F., Rev. of Gastroenterology, 17:359-367 (May), 1950.

Ethically promoted. Available at your druggist in slip-label cartons of 25 envelopes (25 doses).

Chloresium Powder

Natural nontoxic chlorophyll therapy for the treatment of peptic ulcers

FREE—CLINICAL SAMPLE

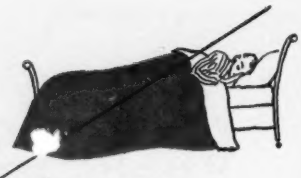
RYSTAN COMPANY, INC. DD-1-P
7 N. MacQuesten Pkwy., Mt. Vernon, N. Y.

Please send full-size sample of Chloresium Powder and reprint of the clinician's paper on chlorophyll therapy for peptic ulcers.

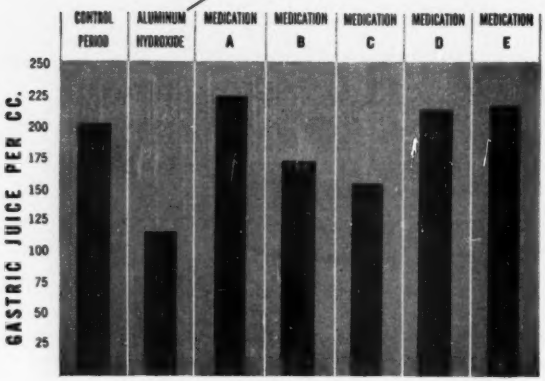
Dr. _____

Street _____

City _____ Zone _____ State _____



No waking with night pain on this ulcer therapy



Average volume of gastric secretion from midnight to 5:30 A.M. in patients with duodenal ulcer treated with various medications *during the day only*. Aluminum hydroxide depresses volume of gastric secretion more effectively throughout entire night period. (Adapted from Brehaus, H. C., Akre, O. H., and Eyerly, J. B.: *Gastroenterology*, 16:172, Sept., 1950.)

By taking Creamalin *during the day only*, the peptic ulcer patient will sleep undisturbed from midnight to morn.

No waking by the alarm clock for medication. Creamalin taken only *during the day and evening* acts all night to produce a marked reduction in gastric secretion.

No waking with night pain. Creamalin is amorphous, acid-soluble reactive, aluminum hydroxide, the most efficient of the alumina gels for prompt and prolonged buffering of acidity.

Creamalin®

(amorphous, acid-soluble, reactive aluminum hydroxide gel)

Creamalin, trademark reg. U. S. & Canada

Winthrop-Stearns INC.

NEW YORK, N. Y. • WINDSOR, ONT.

PEPTIC ULCER IN MAN

PART 4. A NEW ANTACID MADE TO MEET REQUIREMENTS OF ANTACID THERAPY. CHEMICAL AND LABORATORY WORK

H. Necheles, H. Kroll, S. P. Bralow,* and M. A. Spellberg assisted by B. Weiss and K. K. Kushino,
Chicago, Illinois

WE CONSIDER peptic ulcer in man a constitutional disease for which no cure is available as yet, short of leukotomy. The presently employed therapy is therefore symptomatic and, depending on its use, will restore the ulcer patient for shorter or longer periods of time, so he can work and enjoy life. In view of the very large number of ulcer patients, they have been estimated to be 4 million persons in this country (53,-240), and in view of the tremendous loss of time and income caused by this disease, the presently available symptomatic therapy must be taken very seriously, and it must be improved until such time, when the roots of the disease can be treated and its cause can be abolished.

In the search for an ideal antacid, we have studied most of the previous work in this field, have tried to evaluate effects of drugs used in ulcer therapy, and have attempted to establish criteria for comparison of different modes of ulcer therapy (234-236). According to the requirements, which we believe to be important for an ideal antacid, we have developed in the Department of Gastro-Intestinal Research of Michael Reese Hospital a compound, which we feel, comes nearest to the ideal requirements. In this paper the laboratory data on the new antacid are presented. In the following paper, the clinical evaluation will be discussed.

From a series of water soluble polymers tested, sodium carboxymethylcellulose with a high degree of substitution (v. i.) seemed to be most promising and was chosen for further study. Other compounds prepared and tested were sodium carboxymethylstarch, sodium carboxymethylinulin, sodium alginate, and deacetylated chitin.

The use of synthetic polymers as antacids has been described by Martin and Wilkinson (164), and by Segal et al. (161, 162), who used insoluble ion exchange resins for binding the hydrogen ions of gastric juice. Modified natural polymers, such as hog's gastric mucin, have been used for peptic ulcer therapy (76). The latter, a natural high polymer, is a complex mucopolysaccharide. From a purely chemical consideration, the acid combining capacity of native gastric mucin can be attributed to the buffering action of the sodium polyglucuronate portion, to the protein component, and to dialyzable neutralizing substances. It is generally accepted that the mucilaginous and adhering properties of mucin undoubtedly serve as a protective agent against irritation of the gastric mucosa.

The investigation of the various polycarboxylic acids and their evaluation as gastric antacids was motivated by the analogy to the polyglucuronic acid component of gastric mucin. Of the water-soluble sodium polycarboxylates tested, sodium carboxymethylcellulose, containing one carboxymethyl group per glucose unit, i. e. with a degree of substitution varying from 0.3 to 0.5 has found a variety of applications (238), but no investigations were found on its use as a buffer in the therapy of hyperacidity and peptic ulcer.

Chemical and Physical Properties

The carboxymethyl ether of cellulose is prepared by the action of sodium chloracetate on alkali-cellulose, and under controlled conditions it is possible to obtain products having from 0.3 to 2.0 carboxymethyl groups per glucose unit of the cellulose molecule (d.s.=0.3-2.0). The sodium carboxymethylcellulose prepared for these experiments has a d. s. of one, and in the subsequent portions of this paper it will be referred to as *SCMC*.

SCMC is a white hygroscopic solid which dissolves in water to form viscous solutions. The acid, carboxymethylcellulose, has a dissociation constant of 5×10^{-5} (239), and it is not completely liberated from its sodium salt, until the pH is reduced to 2.5. In the reaction of aqueous solutions of SCMC with dilute acids, the polymeric sodium carboxylate behaves in a manner typical of salts of strong bases and weak organic acids. The maximum buffering action takes place between pH 5.5 and 2.5. In our work, the capacity of an antacid was defined as the number of m.l. of 0.1 N hydrochloric acid required to bring the pH of one gram of dry weight of an antacid in solution or in suspension from its initial value down to pH 3.5. For the batch of SCMC employed in this work, the acid combining capacity was 40 m. l. 0.1 N hydrochloric acid. The end point of pH 3.5 was chosen for the following reasons: above pH 3.5 gastric secretion contains no free acid, but only combined acid; peptic activity is low at this pH, and the irritating, corrosive effects of HCl or of gastric juice of pH 3.5 are insignificant in our experience. We feel that complete neutralization of gastric acidity or alkalinization of stomach contents may be actually harmful. This we believe is due to interference with the germicidal barrier of the stomach and to abolition of digestion of protein in the stomach. Also, acid "rebound" may be caused by excessive neutralization.

One of the major objections from the clinical point

From the Department of Gastrointestinal Research of the Medical Research Institute of Michael Reese Hospital,** the Veterans Administration Hospital, Hines, Illinois, and the University of Illinois College of Medicine, Chicago, Illinois.

*Part of a thesis, submitted by Dr. S. P. Bralow, as partial fulfillment for the degree of M. S. (Medicine) from the University of Illinois College of Medicine. Published with permission of the Chief Medical Director, Departments of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors. Dr. Bralow's present address is: Fels Institute, Temple University, School of Medicine, Philadelphia, Pa.

**Supported by a grant from The Ciba Pharmaceutical Co., Inc. The Department is in part supported by the Michael Reese Research Foundation.

of view to most antacids available in tablet form, is their slow rate of neutralization of gastric acidity. This is especially true of preparations containing alumina compounds. In a series of tests carried out on specially prepared SCMC tablets, it was established that the rate of neutralizing dilute acids was reaching its maximum pH level within 10-15 minutes. The reason for the relatively fast action of SCMC is understandable, since the cellulose polycarboxylate may bind the hydrogen by two mechanisms: it may go into aqueous solution and act as a true buffer, i. e., the salt of a weak acid and strong base, or, it may act as anion-exchange substrate while in an insoluble or gel stage, releasing sodium ions in exchange for hydrogen ions of the hydrochloric acid.

As is characteristic of linear polymers, SCMC goes into solution slowly, first passing through a gel stage and then forming a solution of gradually increasing viscosity. The solid material has a great affinity for water, absorbing several times its own weight in the process of solution. The wet SCMC sticks tenaciously to whatever surface it may contact and finally spreads to a smooth viscous layer as the material becomes more hydrated.

IN VIVO STUDIES

Methods: Antacid assays were carried out on dogs weighing from 18 to 35 kgs. The animals had a gastrostomy established (cannula) in the most dependent part of the gastric fundus. The operation is a simple one, leaving the normal blood and nerve supply to the stomach intact, and leaving the continuity and function of the gastro-intestinal tract practically normal. The animals were kept in the laboratory for prolonged periods of time, they were accustomed to the experimental procedures, they were in good health, and they were used exclusively for these assays, performed twice a week in most instances. Food, but not water, was withheld for 24 hours previous to the assay and, immediately before the experiment, their stomachs were washed through the cannula with saline and drained, to assure removal of solid particles. A rubber tube with a clamp was attached to the gastric cannula to facilitate removal of gastric juice and injection of substances into the stomach. Fifteen minutes later, the stomach contents were drawn into a syringe attached to the rubber tubing, the volume noted, a 3 ml. sample retained for a pH determination, and the remainder of the fluid discarded. Then each dog was injected subcutaneously in the dorsal region with 0.6 mgm. of histamine base (dihydrochloride) in 2 m.l. of saline. The antacid was introduced immediately through the cannula and, at 15 minute intervals, the volume of the stomach contents was determined by drawing the liquid into a 100 m. l. syringe, and measuring its volume. The fluid was returned to the stomach except for 3 m.l., which were used for a pH determination. The fluid was returned in order not to remove the antacid to be tested, and in order not to disturb normal mechanisms of the stomach and water-salt balance of the animal. The gastric secretion due to the histamine injection lasted for about 75 minutes and was at its peak 45 minutes after the injection. During the 75 minute interval, the average total secretion obtained per dog varied between 125 to 150 m.l. In the following, the antacid effect of a drug, called the "antacid index," is defined as the number of minutes the stomach pH is maintained above 3.5 during a 60 minute interval after the introduction of the antacid into the stomach. Repeated control tests on the secretory ability of the stomach were performed regularly with histamine only.

The Antacid Properties of a Combination of Sodium Carboxymethylcellulose (SCMC) with Other Acid Neutralizers: The efficiency of an antacid in neutralizing gastric acidity is directly related to the period of contact between the neutralizing agent and the gastric secretions. Antacids are evaluated commonly in terms of the number of m.l. of 0.1 N hydrochloric acid they can buffer or neutralize in vitro, and these values are frequently cited as a measure of the physiological effect of the neutralizing agent. This is a fallacious concept however; although the in vitro acid combining property may be high, a rapid elimination from the stomach will nullify the acid combining capacity of the antacid. Thus, gastric motility and retention of a drug in the stomach are important factors, establishing the length of time a given agent can react in the stomach and determining the *in vivo* efficiency of the antacid.

The following experiments were designed to illustrate the property of sodium carboxymethylcellulose of forming a retentive coating on the gastric mucosa which could not be eliminated readily. To achieve this purpose, a 10% solution of sodium carboxymethylcellulose** with a low d.s. of 0.5 was used to prepare antacid compositions containing 1% sodium bicarbonate and a 1% dispersion of calcium carbonate respectively. Low d.s. SCMC was employed as a retaining vehicle, in order to test neutralizing effects of the added substances rather than buffering effects of the SCMC. A 10% solution of the sodium carboxymethylcellulose alone, a 1% aqueous solution of sodium bicarbonate, and a 1% suspension of calcium carbonate in water were used as control.

Fifty m.l. samples of these preparations were assayed on the gastrostomy dog by the method described above. The data obtained in these assays are presented in Table I. These data illustrate the affinity of sodium carboxymethylcellulose solutions for the gastric mucosa, as indicated by the prolonged neutralizing effect of sodium bicarbonate and calcium carbonate in the presence of the polymer. A number of other substances were tested in the same way, and it appears that all antacids and alkalis will react similarly to calcium carbonate or sodium bicarbonate, when retained in the stomach by SCMC. Finally, magnesium oxide was chosen as component for SCMC tablets (see Fig. 3 below).

TABLE I

THE ANTACID PROPERTIES OF 10% SCMC, D. S. = 0.5 SOLUTIONS CONTAINING ACID COMBINING AGENTS

	Composition	No. of Dogs	Antacid Index* (Minutes)
1.	10% SCMC	16	0
2.	1% aqueous sodium bicarbonate	16	0
3.	1% aqueous sodium bicarbonate plus 10% SCMC	16	52
4.	1% calcium carbonate dispersion in water	16	24
5.	1% calcium carbonate dispersion plus 10% SCMC	16	40

*The number of minutes during which the stomach pH is maintained at or above 3.5 after the introduction of the antacid.

ANTACID ACTIVITY OF SCMC

In the previous section, the enhancing effect of a low viscosity sodium carboxymethylcellulose solution, d.s. = 0.5, on the in vivo acid combining properties of sodium bicarbonate and calcium bicarbonate was described. In these experiments, the cellulose polymer per se was devoid of observable antacid effect because

**Supplied by the Dow Chem. Co. as Sodium Carboxymethocel.

TABLE II

ANTACID PROPERTIES OF SCMC SOLUTIONS, D.S. = 1

Composition	No. of Dogs	Antacid Index (Minutes)	
		25cc.	15cc.
25% SCMC	24	52	41
20 SCMC	16	47	34
15% SCMC	16	38	15
Antacid* A	8	54	34
Antacid B+	8	43	35

*aluminum hydroxide gel.
+Aluminum hydroxide-magnesium trisilicate suspension.

of its low degree of substitution. In the data presented in *Table 2*, 25, 20 and 15% aqueous solutions of SCMC d.s. = 1 were prepared; 25 m.l. and 15 m.l. portions were introduced into the stomach of the assay dogs, and antacid activity was determined. Two commercial aluminum hydroxide preparations were used for comparison. The data in Table 2 indicate that the SCMC of d.s. = 1, by itself, exerted a considerable buffering effect against a constant flow of gastric secretion from the histamine stimulated dog's stomach. The concentration of the polymer required to exert an effect equivalent to aluminum hydroxide gel was relatively high; however, SCMC is a bland non-irritating substance, which does not constipate as many antacids do, and which is able to relieve constipation when given in sufficient quantity. This will be discussed below.

THE ACID-BASE BALANCE IN DOGS RECEIVING SCMC SOLUTIONS

The effect of daily oral administration of SCMC on the acid-base balance of dogs was determined in order to establish whether the antacid would produce an alkalosis. From theoretical considerations and from the experience of others (246) it was postulated that the polymeric cellulose derivatives are not absorbed from the gastro-intestinal tract and that a normal acid-base balance would be maintained.

Four dogs received 50 ml. solutions daily of a 25% SCMC d. s. = 1 by instillation through the stomach cannula over a period of six weeks. Weekly samples of venous blood were withdrawn and whole blood pH, plasma chlorides, and plasma carbon dioxide, were determined. Appearance and behavior of the animals showed no change, and the data obtained showed normal values for all dogs. It can be concluded that, during the test period, there was no deviation from the normal blood values, and that no sign of alkalosis was apparent. Similar experiences on the rat are reported below.

EFFECT OF SCMC ON HISTAMINE-BEESWAX INDUCED ULCERS IN DOGS

A modification of the method of Code et al. (241) was used for producing experimental ulcers in dogs. Preliminary work indicated that there was considerable variation in response to the histamine-beeswax mixtures, and therefore the following procedure was adopted. Healthy male and female mongrel dogs were used. Each dog was given an intra-muscular injection in the dorsal region of the beeswax preparation, containing 15 mgms. of histamine base, once daily for five days. This was followed by a daily injection, containing 30 mgms. of histamine base for nine days. Animals that

TABLE III

EFFECT OF SCMC ON HISTAMINE-BEESWAX INDUCED ULCERS IN DOGS

Category	Controls		Treated	
	No. of Dogs	Pct.	No. of Dogs	Pct.
A. Death due to ulcer	4	16.5	0	0
B. Dogs with ulcer	16	67.0	3	21.3
C. Dogs with no ulcer	4	16.5	11	78.7

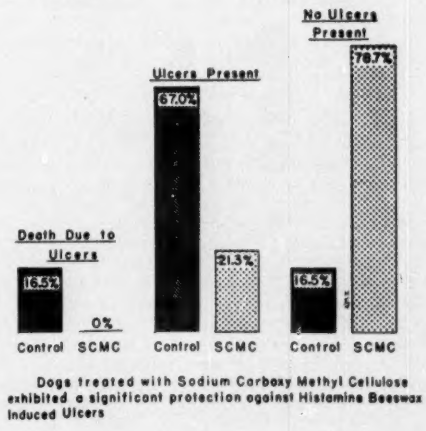
died during the course of the experiment were autopsied. At the end of the 14 day period the surviving dogs were sacrificed, and autopsies were performed. In earlier experiments, the introduction of the antacid via stomach tube was attempted, but this was abandoned since the oral introduction of the stomach tube twice daily had deleterious effects on the dogs, weakened by histamine-beeswax injections. Therefore the animals were prepared with gastric cannulas for introduction of the antacid and were used exclusively for these experiments. The introduction of the antacid into the stomach via the cannula could be accomplished without the risk of producing anoxia, aspiration, excitement, and struggle on the part of the dog. On the basis of the post mortem findings, the dogs were divided into three categories, presented in *Table 3 and in Fig.* 1. A. Dogs whose deaths were due to gastric or duodenal ulcer. B. Dogs with ulcer. C. Dogs with no ulcer.

In the control series, 24 dogs were submitted to the histamine-beeswax procedure, as described in the previous paragraph. At the conclusion of the two week period, the dogs were sacrificed and autopsied.

In the SCMC treated series, fourteen dogs with gastrostomy cannulas were used. One ounce of a 20-25% solution of SCMC d.s. = 1 was administered twice daily, morning and late afternoon. The histamine-beeswax mixture was injected immediately after the antacid dose in the morning.

The procedure of histamine-beeswax administration

Figure 1



produced gastro-intestinal ulceration in 67% of the control dogs. In the treated series, there was a significant decrease in the number of dogs which exhibited gastrointestinal damage, 21.3%. The SCMC seemed to protect against the histamine-beeswax injection. Death due to ulcer was observed in 16.5% of the untreated animals, but in none of the SCMC treated animals. It is emphasized that, although the treated dogs showed greater resistance to gastro-intestinal ulceration, they exhibited the same marked symptoms of histamine poisoning as observed in the control series. These symptoms were characterized by loss of appetite, general weakness, and a number of deaths, before the two week test period elapsed.

HEALING EFFECTS OF SCMC

An effort was made to determine whether sodium carboxymethylcellulose has a local healing effect on peptic ulcer. It was found difficult, however, to determine the daily rate of healing in a lesion of the stomach or duodenum, and therefore it was felt that the material should be tested for a possible healing effect on superficial skin wounds (247). Such an effect is to be considered only as an indication of healing properties of the drug in the case of ulcer, without assuming that the healing of a peptic ulcer is analogous to that of skin. Circular wounds approximately 1.0 sq. cm. in area were made on each flank of young guinea pigs, and a doughnut-shaped lucite ring was glued tightly to the skin surrounding the wound, to prevent most of the contraction phase of wound healing. It was found that 1.8 per cent sodium carboxymethylcellulose with 0.6 per cent magnesium oxide showed 100 per cent healing within 8.7 days, as compared to 11.7 days for the control wounds treated with methylcellulose (Fig. 2). This significantly increased rate of healing may be attributed to an alkaline pH and to the fact that sodium carboxymethylcellulose may serve as a supporting base for epithelial cell movement, facilitating the expansion of the epithelial membrane (247).

SCMC as Laxative—Carboxymethylcellulose belongs to a group of hydrophilic colloids and therefore, in the process of going into solution, it absorbs several times its own weight of water. This marked affinity for water moderately softens the feces, and tends to produce a viscous lubricant medium. Hence, medication is not only non-constipating but also conducive to normal elimination. These advantages represent an addition to the treatment of ulcer patients, many of whom are notoriously constipated.

To confirm our clinical finding that sodium carboxymethylcellulose acts as an efficient bulk laxative, studies were made on the water content of rat's feces.* A 70 per cent increase in the water content was observed after sodium carboxymethylcellulose intake. The average weight of the feces without sodium carboxymethylcellulose in the diet was 6.2 grams for 24 hours, and when sodium carboxymethylcellulose has been added to the diet, the average weight of the feces increased to 10.5 grams, i.e. by 70%. No adverse effects of prolonged administration of the drug to the health or to the blood chemistry of the rats were noted, particularly no significant loss of calcium.

TABLET COMPOSITION

The buffering effects of experimentally prepared tablets of SCMC, d. s. = 1, in normal gastric juice were apparent within 10 minutes and reached a maximum within 20 minutes. However, in the case of ulcer pain or distress the patient expects more immediate

*Dr. W. L. Loewe of the University of Utah Medical School was kind enough to supply us with the data of his studies on the blood chemistry and on the water content of the feces of rats, when fed SCMC in their diet.

Figure 2

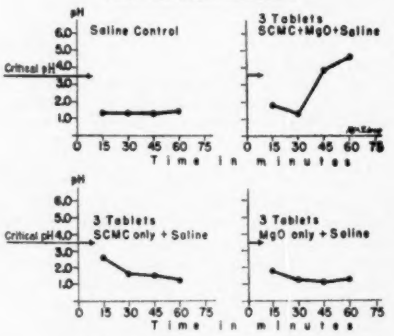
Effect of Sodium Carboxy Methyl Cellulose On Healing Of Skin Wounds (guinea pigs)

Days	Size of Skin Wounds: Untreated Controls	SCMC 1.8% Applied to Wounds	SCMC 1.8% With 0.6% MgO Applied to Wounds
8	51%	90%	94%
9	70%	Healed	Healed
10	79%		
11	90%		
12	99%		
13	Healed		

Sodium Carboxy Methyl Cellulose aids epithelialization, apparently produces a favorable mild alkaline ph, and may also serve as a supporting base for epithelial cell movement.

Figure 3

The Potentiating Buffering Effect of Sodium Carboxy Methyl Cellulose Plus Magnesium Oxide



Effect on gastric acidity: Tablets of 450 mgms of Sodium Carboxy Methyl Cellulose combined with 150mgms of Magnesium Oxide are compared with separate tablets of each of these components and to a Saline Control as tested on dog's gastric secretion stimulated with histamine.

relief. Therefore, a small quantity of magnesium oxide was added to the tablet compostion, to act as "ignition" neutralizer. Each tablet contained 450 mg. of sodium carboxymethylcellulose and 150 mg. of magnesium oxide. Magnesium oxide in that dose was found to have no neutralizing effect on the histamine stimulated gastric acid secretion of the dog. However, the retentive and coating effect of SCMC made small quantities of inorganic neutralizing substances dramatically effective. This is demonstrated in Fig 3. Tests were made with tablets of sodium carboxymethylcellulose-magnesium oxide, sodium carboxymethylcellulose alone, and tablets of magnesium oxide alone. It was found that the small amount of magnesium oxide (150 mg) potentiated the buffering capacity of sodium carboxymethylcellulose, i. e. the buffering capacity of the two agents is greater than can be accounted for by a mere summation of effects. This was studied further on several healthy adults, and the combination of sodium carboxymethylcellulose and magnesium oxide produced a more rapid decrease of acidity and maintained it longer than either agent alone. A further increase in effectiveness of SCMC as neutralizer was attained by adding small amounts of oil of peppermint to a 5% solution of SCMC. In the greater number of tests with this combination, using gastrostomy dogs, a diminution in the volume of stomach juice was noted in addition to the neutralizing effect. SCMC by itself produced a similar though smaller decrease in volume of gastric juice in tests on man and on dogs. We are not in a position to explain this observation completely. Previously, we have described depression of gastric acid secretion and shorter emptying time of the stomach with oil of peppermint (243-245). Also, we have reported earlier, that mucilagenous substances per se can shorten the emptying time of the stomach (242). In the present work, we have tested a number of antacids which are used frequently in the treatment of ulcer, and we have the impression that some of their effectiveness in the relief of ulcer distress is due to the oil of peppermint contained in them.

SOLUBILITY OF SCMC-MgO TABLETS

Throwing a tablet of a drug preparation into a glass of water and marking the time of complete disintegration does not indicate what happens in the stomach after such a tablet has been swallowed. Therefore, the following procedure was employed. 50 m.l. portions of 0.1 normal hydrochloric acid or of natural gastric juice were placed in Erlenmeyer flasks, and the flasks were placed in a water bath at 37°C. One SCMC-MgO tablet was placed in each of the flasks, and the flasks were rotated mechanically, making two rotations per minute. The motion caused the contents of the flask to make one revolution with each complete turn of the flask. Each tablet from different batches was tested 4 times. No significant difference was found in the rate of solution of the tablets tested. The following behavior was typical: the tablets in about half of the trials stuck to the walls of the flask, while the others floated on the surface of the acid. The tablets swelled and presented a jelled appearance. After about 30 minutes all of them had spread out over the surface of the glass. At the end of one hour, about one third to one half of the tablet had dissolved, and the residue remained as a soft lump on the glass.

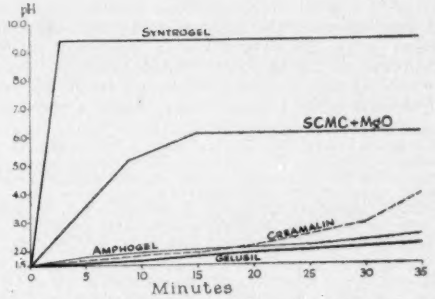


Fig. 4 Rate of Neutralization of HCl by Various Antacids. The pH values between 3.5 and 5.5 are considered to be the physiological range within which an antacid should buffer gastric acidity.

As we have explained above, gastric acidity is reduced, even before the SCMC-MgO tablet goes into complete solution. This is due to the rapid neutralizing effect of the magnesium oxide, and to the fact that the sodium carboxymethylcellulose (SCMC) exchanges sodium ions for hydrogen ions while still in the gel stage. A number of commercial antacid tablets were tested for speed of disintegration by the above described method, and the following values were obtained: hydrated alumina tablets and Syntrogel, instantaneous; Creamalin, 35 to 45 minutes; and Gelusil, 45 to 50 minutes. We believe that rapid decomposition of tablets in the stomach and the presence of a high degree of alkalinity within a small area, may be detrimental.

The neutralizing effect in vitro of the sodium carboxymethylcellulose-magnesium oxide tablet was determined, by recording the change in the pH of 25 m.l. of dilute hydrochloric acid of pH = 1.5, following introduction of the tablet. The solutions were agitated mechanically at 5 minute intervals. The data in Fig. 4 show that the SCMC-MgO tablet neutralized at a rather rapid rate, without producing undue alkalinity, when compared with other tablet antacid preparations. We believe that an ideal pH in cases of peptic ulcer should be between 3.5 and 5.5; such pH would not abolish digestion and peptization of proteins, and would be neither too acid nor too alkaline, considering the physiological conditions of the stomach.

COATING EFFECTS OF SCMC-MgO TABLETS

Sodium carboxymethylcellulose rapidly forms a protective demulcent coating over the gastric and duodenal mucosa and ulcers, and the layer adheres tenaciously. The persistence of this layer has been noted in man through the gastroscope for as long as three hours after ingestion of the tablets. This adhesiveness renders the material an excellent carrier of an adjuvant antacid such as magnesium oxide, or an antispasmodic. Trasentine, which is a local anesthetic agent as well as an antispasmodic, is only slowly released from the gelatinous vehicle, and its effectiveness is thereby increased.

Gastroscopic studies were performed on four patients; three with large observable gastric ulcers, and one with a gastro-enterostomy and suggestive marginal ulcer. An attempt was made to determine whether

the sodium carboxymethylcellulose actually coated the ulcerated lesion. Differentiation of this material from normal gastric mucus was made in these cases on the appearance of glaring white gelatinous material which represented sodium carboxymethylcellulose, whereas normal mucus had a grayish-white, watery appearance.

Case No. 1—X-ray showed a large posterior gastric ulcer on the lesser curvature. He was gastroscoped 75 minutes after swallowing 3 tablets of SCMC-MgO, and projecting white deposits of SCMC were noted in the crater. Re-gastroscoped after 5 weeks of SCMC-MgO treatment, 80 minutes after ingesting 3 tablets, a much smaller crater was seen in the same location as previously, filled with particles of SCMC.

Case No. 2—X-ray showed a large gastric ulcer on the lesser curvature of the pars media. Gastroscopy revealed the lesion covered with grayish mucus. Re-gastroscoped 160 minutes after 3 tablets of SCMC-MgO, pearly white specks of SCMC were seen in the crater, fundus, and along the rugi.

Case No. 3—X-ray showed an anterior wall gastric ulcer. Gastroscoped 120 minutes following ingestion of 3 tablets of SCMC-MgO. The crater was filled with white SCMC. Two of the tablets were still undergoing disintegration in the fundic portion.

Case No. 4—Old gastroenterostomy for duodenal ulcer. Gastroscopy showed marginal ulcer. Repeat gastroscopy, 160 minutes after 2 tablets of SCMC-MgO, demonstrated glaring white strands of SCMC about the stoma (see also 248).

Similar results with gastroscopies have been reported by Brick (249). Our gastroscopic tests on man were confirmed in experiments on dogs. Six normal starving dogs received 1 or 2 tablets of SCMC-MgO with an ounce of water, or 1 ounce of a liquid 5% SCMC by mouth. One and two hours later, they were sacrificed. Stomach and duodenum were taken out, opened, stretched out in a basin, and a 5% solution of copper sulfate was sprinkled over the mucosa. One hour later, the copper sulfate had stained the sodium carboxymethylcellulose green. In 5 out of 6 experiments most of the gastric and duodenal mucosa were found to be coated with the sodium carboxymethylcellulose. In one experiment the tablets had been caught in swallowed hair, and the hairball and surrounding mucosa were coated with the SCMC. Bile and mucus reacted with the copper sulfate, but the resulting blue colors could be differentiated from that of the green SCMC.

DISCUSSION

The use of SCMC preparations as a gastric antacid and coating substance introduces a new mode of therapy for hyperacidity and peptic ulcers. The mechanism of its action is essentially that of substituting a weak acid for the strong hydrochloric acid of the stomach, plus the added effect of the buffering action of the salts of the weak acid. As a result of this transformation, the irritating effect of the acid on ulcerations is alleviated and, since the stomach pH is raised above 3.5, the proteolytic action of pepsin is depressed. Because of the high molecular weight of SCMC and its resistance to intestinal enzymatic degradation, the antacid passes through the intestinal tract intact, except for reactions involving the acid binding carboxyl group. It should be pointed out that the exchange of the sodium ions in SCMC for the hydrogen ions in the stomach is reversible, and the alkaline duodenal secretions are capable of converting the carboxymethylcellulose formed in the stomach to the sodium salt.

Another characteristic, which distinguishes SCMC from other nonsystemic antacids such as alumina, calcium carbonate, and magnesium trisilicate, is its complete solubility in neutral and acid secretions. The solutions vary from gelatinous masses to viscous compositions, which display an affinity for coating the gastric and duodenal mucosa. It is believed that the coating of the mucosa with SCMC is responsible largely for neutralizing the acid secretion. There is indication from our data that the presence of SCMC in the stomach diminishes the volume of gastric secretion. Further verification of the observation is necessary, but it can be said that with the procedure used in our experiments, the fluid volumes in the dogs' stomachs treated with SCMC were always less than the histamine controls in the same animals, and less than the values in the same dogs treated with other antacids.

The non-toxicity of SCMC is of importance in respect to its use as an orally administered therapeutic agent. Sodium carboxymethylcellulose having a degree of substitution from 0.3 to 0.5 has been used as a thickener for foodstuffs since 1924. In our laboratory, experimental animals have received large doses of SCMC for periods of time extending over eighteen months, remaining in excellent health throughout the experiment.

A drawback in most presently used modes of antacid therapy is the constipating action of many of the agents used. SCMC, because of its inability to diffuse through the intestinal wall, exerts an osmotic effect in keeping fluid in the intestine, or in drawing fluid into the intestine. Probably, it also lubricates hard feces. Accordingly, SCMC functions as a bulk laxative.

A preparation has been available commercially, based on the work presented above. The preparation has been given the trade name Carmethose* The tablets were made in a smaller size than those used in our work, because some patients complained about the size of the tablet, and occasionally about a sticking sensation in their esophagus after swallowing the tablet. Each Carmethose tablet contains 225 mgm of SCMC and 75 mg of magnesium oxide (half the amounts of each drug used in our study). A liquid preparation of a pure 5% SCMC was also made available. The d.s. of the SCMC used in these drugs is approximately one. The neutralizing ability of 1 gram of the SCMC used in the preparation of Carmethose was 28 m.l. of 0.1 N H Cl, upon electrometric titration up to pH of 3.5 of the solution. The in vitro solubility of the earlier preparations of Carmethose tablets was slower than the solubility of the laboratory prepared SCMC-MgO tablets. However, in vivo, dissolution of the Carmethose tablets in dogs and in man (during gastroscopy) was observed to occur within 30 to 60 minutes. Clinical results obtained with Carmethose tablets appear to be as satisfactory as with the larger tablets which were used in the above work.

SUMMARY

The use of sodium carboxymethylcellulose, having one sodium carboxymethyl group per glucose unit, has been investigated as an antacid for the therapy of hyperacidity and peptic ulcer. Studies on normal subjects, on patients, in vitro studies, assays on gastrostomy dogs, and on dogs with histamine beeswax ulcer were performed. Accessory studies were done on guinea pigs and rats. The results indicate that sodium carboxymethylcellulose is an efficient neutralizer of gastric acidity, that it protects dogs against histamine beeswax ulcer, and that it does not constipate, but acts as a bulk laxative. It functions chiefly as a non-systemic buffer

*Ciba Pharmaceutical Co. Inc.

in neutralizing gastric secretions. It has the property to stick to the gastric and duodenal mucosa and form a viscid, protective coating. It retains antacids like carbonates or magnesium oxide, and spasmolytic drugs, for prolonged periods of time in contact with the gastric and duodenal mucosa, and makes these adjuvants more effective than if they were given alone.

The complete bibliography will appear with the next paper of this series.

PEPTIC ULCER IN MAN

PART 5. A NEW ANTACID, SCMC, MADE TO MEET REQUIREMENTS OF ANTACID THERAPY. CLINICAL EVALUATION

S. P. BRALOW,** M. SPELLBERG, H. KROLL, AND H. NECHELES, Chicago, Illinois.

THIS STUDY was undertaken to evaluate clinically the efficacy of a new synthetic antacid, sodium carboxymethylcellulose (SCMC). To achieve the theoretical qualifications for an ideal antacid, this material was prepared to satisfy the following requirements: to be bland and not constipating; non-absorbable, not affecting the acid base balance; to coat the stomach and duodenum with a protective mucoid layer; to be a buffer which stays on the gastric and duodenal mucosa for a prolonged period of time; and to act as a carrier of other drugs which would stay longer in the stomach with the combination than by themselves, such as magnesium oxide or other antacids, or antispasmodics that have surface anesthetic properties, such as Procaine or Trasentine (250). Each tablet of the preparation of SCMC contained 450 mgm. of the drug with 150 mg of magnesium oxide. The considerations which led to the elaboration of this drug, and the laboratory study of this drug and its combinations, have been discussed in previous papers (234-237).

For the purpose of the present work we had to compare the rates of recurrence in similar groups of patients on different therapeutic regimes. The Veterans Administration Hospital, Hines, Illinois, was selected as it was felt that at this institution a large and rather uniform series could be followed and compared with a similar control group treated by the usual regimen, and with preparations of aluminum hydroxide.

All peptic ulcer patients at Hines Hospital were placed on a graduated Sippy type diet. During the active treatment when the patient was at bedrest, he was fed only cereals, gelatin, boiled eggs, and milk and cream. This was divided into six feedings; breakfast, 10:00 a.m. feeding, dinner, 2:30 p.m. feeding, supper, and at 10:00 p.m. feeding. The experimental patients were not given the hourly milk and cream that the control patients had. This was done to evaluate whether the new therapy had any clinically significant duration of activity. After about one week of active treatment, almost all the patients were improved enough to be allowed bathroom and mess hall privileges. They then were allowed a more liberal type of diet, Gastric No. 2. If, after another week they were able to tolerate this increase, they were allowed full ambulatory privileges as well as a Gastric No. 3 diet, which included meat. In the absence of complications, on a Gastric No. 3 diet, the patient was discharged after about three weeks total hospitalization. The only deficiency noted on this dietary regime was during the Gastric No. 1 period, when the diet was considered low in niacin and ascorbic acid. If this diet was continued for more than one week, supplemental vitamins were given.

Method of Study—The experimental group of patients, that is those treated with the new preparation, consisted of 127 consecutive patients admitted to the Gastrointestinal Section of the Veterans Administration Hospital, Hines, Illinois. No attempt as to selection of patients was undertaken other than the fact that the patient was suffering from peptic ulcer. Definite radiographic evidence of ulcer was obtained in all but fifteen patients. There were 94 patients with duodenal, 15 with gastric, 1 with post-bulbar, and 2 with both gastric and duodenal.

This group was treated with tablets of sodium carboxymethylcellulose, 450 mgms and magnesium oxide, 150 mgms. These patients were immediately placed at bedrest on arrival to the ward and given the above medication, a routine of one tablets four times a day and two at bedtime. Tablets were administered between meals to coincide with the supposed peak of gastric acidity. This timing of administration is considered to be an important factor in treatment (196). A maximum dose of one tablet every two hours and two at bedtime was given the more resistant patients. Mild sedation was given as a routine, but antispasmodics were not given except in a few cases which presented evidence of pylorospasm or obstruction. These latter patients were aspirated each night to check retention, and were given tablets of SCMC-MgO containing 75 mgms of Trasentine for limited periods of time. The duration of the special treatment varied for each patient according to his response, and ranged from two to sixty days.

After discharge from the hospital, the patient was advised to continue on the management until he was re-evaluated after one month and after three months of ambulatory treatment. At the first check-up, a re-

From the Veterans Administration Hospital, Hines, Illinois, from the Department of Gastrointestinal Research, Medical Research Institute of Michael Reese Hospital,* and from the University of Illinois College of Medicine, Chicago, Ill.

**Part of a thesis, submitted by Dr. S. P. Bralow as partial fulfillment for the degree of M. S. (Medicine) from the University of Illinois College of Medicine. Published with permission of the Chief Medical Director, Departments of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors. Dr. Bralow's present address is: Fels Institute, Temple University, School of Medicine, Philadelphia, Pa.

*Supported by a grant from The Ciba Pharmaceutical Co., Inc. The Department is in part supported by the Michael Reese Research Foundation.

peat gastric analysis was done in an attempt to evaluate objective changes, but no clearcut information could be obtained by this procedure. A repeat gastro-intestinal roentgenogram was taken three months after discharge, and if evidence pointed to arrest of ulcer activity, medication was interrupted. The patient was advised to continue his diet for one year and to avoid stimulants. He was also instructed to report back immediately if symptoms recurred, at which time he was restarted on medication. Re-evaluation was again attempted after nine months by simple questionnaire, which supplied satisfactory information as to recurrences (8-10, 203, 204).

For the control series, similar questionnaires were forwarded to 180 consecutive peptic ulcer patients, treated with aluminum hydroxide preparations on the same ward by the same consultant during the year prior to the start of the special study. Of these 180 patients, 100 answered, each of whom was then followed for one year. This number of patients was felt to be sufficient for comparison with the experimental group. The control group was not called in for re-evaluation by roentgenograms.

The incidence of the different types of ulcer in the control group was quite comparable to that in the experimental series; 74 with duodenal, 15 with gastric, 3 with marginal, and 8 with tenable clinical diagnosis of ulcer, but with negative radiological studies.

CRITERIA OF RECURRENCE

The criteria of recurrence or failure of therapy have been discussed in a previous paper (236). Any patient, after obtaining a complete remission on hospital therapy, who manifested signs or symptoms warranting readmission to the hospital, such as perforation, bleeding obstruction, or intractable pain, was considered a recurrence. The mere presence of epigastric distress which could be relieved by further antacid or diet therapy was not so considered.

RESULTS

Both the control and the experimental series were subdivided according to the location of the lesion as well as chronicity of the lesion.

Arbitrarily, those ulcers were called chronic that had a three year history of verified ulcer complaints, because the response of an ulcer to treatment has been reported to vary according to the duration of symptoms. In *Table No. 1*, the average duration of symptoms for the experimental series is shown to be 8.8 years, and this same average was found in the control series. Seasonal recurrences were noted in 58% of the experimental series; 73% had periodicity of pain; 79% reported relief of symptoms by foods; and 77% complained of night pain at time of admission. These values indicate the significance of these often described characteristic symptoms of peptic ulcer and compare favorably with the experience of Bockus (101).

Of 129 patients treated with SCMC-MgO tablets, 20 were completely uncooperative, and four others had to be discarded because other pathology emerged, such as coronary disease, tuberculosis, and bronchogenic carcinoma, thus leaving 105 patients followed actively.

There were 94 patients, with an average age of 43 years, suffering from duodenal ulcer. Of these, 68 had histories of over three years' duration. During the year studied, 12 of these chronic patients were discarded because of poor cooperation, and 17 patients or 25%

TABLE I

DURATION AND FREQUENCY OF SYMPTOMS IN PATIENTS TREATED WITH SCMC-MgO TABLETS AND IN A CONTROL GROUP

Ulcer	Duration of Symptoms Years	Total No. of Patients	Average Duration and Range of Symptoms		No. e. Season. Recurr.	No. e. Periodicity of Pain	No. e. Relief by Food	No. e. Night Pain
			SCMC-MgO	Control				
Duodenal	1-3	26	1.4 yrs. (1-33 mos)	1.6 yrs (1 day-3 yrs)	14	22	21	16
	+3	68	12.2 yrs (3-40 yrs)	11.9 yrs (3-31 yrs)	30	30	40	39
	Total	94	8.9 yrs (1 mo-40 yrs)	9.3 yrs (1 day-31 yrs)	44	52	61	55
Gastric	1-3	5	0.1 yrs (2 wks-29 yrs)	0.5 yrs (2 days-2yrs)	3	3	2	5
	+3	10	15.8 yrs (3-29 yrs)	10.4 yrs (3-29 yrs)	5	6	4	6
	Total	15	10.6 yrs (2 wks-29 yrs)		8	9	6	11
Marginal	+3	2	20 yrs (15-25 yrs)	15.3 yrs (3-28 yrs)	1	0	0	1
Clinic. posit. X-ray negat.	+3	15	9.3 yrs (3-27 yrs)	8.3 yrs (7 mos-27 yrs)	5	10	10	8
Post-Bulbar	1-3	1	5 yrs		0	1	1	1
Gastr. & Duod.	3	2	11.5 yrs. (4-19 yrs)		1	1	1	1
Totals		129	8.8 yrs (2 wks-40 yrs)	8.8 yrs (1 day-31 yrs)	59	73	79	77

had to be re-hospitalized; 5 with hemorrhage, 1 with perforation, and 11 with intractable pain. Surgery was performed in 7, and 3 of these died. Although the discarded uncooperative cases were not, as far as is known, readmitted to any hospital, they might be considered as failures for the present treatment, and thus would raise the recurrence rate for this group to 42%.

Inasmuch as this group of ulcer patients made up over ½ of the entire series, thus exerting a marked influence on the overall statistical results, it is interesting to note that this group also presented histories of previous severe complications: hemorrhage in 27, previous perforation in 2, and previous surgery, type unkown, in 7. Ulcer patients with this type of background do notoriously poorly on any type of management. Therefore, it was felt that this group offered a severe test for the investigated medication.

Of the 26 acute cases of duodenal ulcers, 8 were discarded because of poor cooperation. Only 4 patients had to be readmitted, or 15% of the total. However, if the discarded cases are added, the recurrence rates would be 22%. History in these patients revealed that 5 had previous hemorrhage, and only 1 had previous surgery. On SCMC-MgO therapy only one of the 4 readmitted patients had a hemorrhage, and none required surgery.

Fifteen patients had gastric ulcers, and in 10, the duration of symptoms was over 3 years. Of the chronic group, 2 had previous surgery for perforations, and 4 had had hemorrhages. For the acute series, only 1 hemorrhage was reported. Surgery was performed in 2 of the acute and in 4 of the chronic gastric ulcers, because of the difficulty to rule out gastric carcinoma. If malignancy was found, the patient was not included in our statistics. The recurrence rate of each of the subgroups was approximately 20%.

There were 2 marginal ulcers, one post-bulbar, and 2 combined gastric and duodenal ulcers, in the series. Fifteen patients were included who did not show definite roentgenographic evidence of ulcer, but the clinical picture was thought to be consistent with such a diagnosis. All of the patients without radiographic confirmation had histories of over three years' duration; 6 had previous hemorrhages, and 1 had a history of perforation. On admission, six of these unconfirmed patients had hemorrhages; one had intractable pain, and eight had tractable pain. St. John (9) has stated that between 10 to 20% of patients with the clinical diagnosis of ulcer have symptoms of more than mild degree without demonstrable lesions. This is substantiated by the incidence of such cases in our series. All of these 20 patients in the subgroups were kept asymptomatic on SCMC-MgO medication.

From the complete series of 129 patients, 24 were discarded because of lack of cooperation or other pathology, and of the remaining 105 patients, 23.8% were readmitted during the one year follow-up; 6.6% with hemorrhage; 0.9% with perforation; and 16% with intractable pain. Fourteen patients required operations for signs of obstruction during the year study; of these, 3 died (Table No. 2).

TABLE II

PEPTIC ULCER PATIENTS TREATED WITH SCMC-MgO TABLETS, STUDIED FOR A PERIOD OF ONE YEAR

			HISTORY			Patients Rehosp. & Reasons				During One Year		Study
Ulcer	Duration Symptoms Years	Total No. Pts.	Age (Yrs)	Complications	Sympt. at Present Admission	Totals No.	Hem.	Perf.	Intract. Pain	Operat.	Deaths	Discard.
Duoden.	1-3	26	37.2 (21-55)	Hemorrh. 5 Intr. Pain 6 (Surgery 1)	Hemorrh. 6 Intr. Pain 3 Tract. Pain 14	4 (15%)	1	0	3	0	0	Uncoop. 7 other path. 1
	+3	68	43.1 (24-72)	Hemorrh. 27 Perfor. 2 Obstr. 2 (Surgery 7)	Hemorrh. 24 Intr. Pain 19 Tract. Pain 20	17 (25%)	5	1	11	7	3 ulc. 4 other path.	Uncoop. 11 other path. 1
Gastr.	1-3	5	47.6 (32-63)	Hemorrh. 1	Hemorrh. 2 Intr. Pain 1 Tract. Pain 1 (Surgery 2)	1 (20%)	0	0	1	2	0	0
	+3	10	53.4 (41-60)	Hemorrh. 4 Perfor. 2 (Surgery 2)	Hemorrh. 2 Intr. Pain 6 Tract. Pain 2 (Surgery 4)	2 (20%)	0	0	2	4	0	0
Margin.	+3	2	56.5 (55-58)	Hemorrh. 2	Intr. Pain 1 Tract. Pain 1 (Surgery 1)	1 (50%)	1	0	0	1	0	0
Clin. Posit. X-ray negat.	+3	15	36.4 (22-52)	Hemorrh. 6 Perfor. 1	Hemorrh. 6 Intr. Pain 1 Tract. Pain 8	0	0	0	0	0	0	Uncoop. 1 other path. 2
Post-bulbar	1-3	1	44	Hemorrh. 1	Hemorrh. 1	0	0	0	0	0	0	0
Gastr. & Duoden.	1-3	1		Hemorrh. 1	Hemorrh. 1	0	0	0	0	0	0	Uncoop. 1
	+3	1	61	Hemorrh. 1	Hemorrh. 1	0	0	0	0	0	0	0
Total Total cooper.		129 105	Av. 51	Hemorrh. 48 Intr. Pain 6 Perfor. 5 Obstr. 2 (Surg. 10)	Hemorrh. 43 Intr. Pain 31 Tract. Pain 46 (Surg. during hosp. 7)	25 23.8%	7 6.6%	1 0.9%	17 16%	14 13%	3 2.9% 4 other path.	Uncoop. 20 other path. 4 24

TABLE III

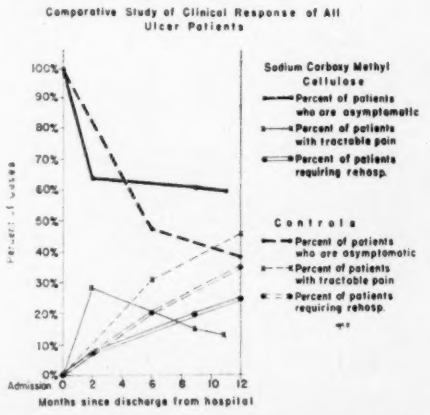
PEPTIC ULCER PATIENTS TREATED WITH ALUMINUM HYDROXIDE, STUDIED FOR A PERIOD OF ONE YEAR

Ulcer	Duration Symptoms Years	Total No. Pts.	Age (Yrs)	HISTORY Complications	HISTORY Sympt. at Present Admission	Pts. Rehosp. & Reasons Total No.	Hem.	Perf.	Intr. Pain	During 1 Year Study Operated	Deaths
Duoden.	1-3	20	39.8 (18-60)	Hemorrh. 2 Perfor. 3 Intr. Pain 2	Hemorrh. 8 Intr. Pain 6 Tract. Pain 7 Death 1	8 (40%)	1 (died)	0	7	1 hemorrh.	2
	+3	54	42.6 (22-68)	Hemorrh. 16 Perfor. 8 Intr. Pain 18 (Surgery 6)	Hemorrh. 22 Intr. Pain 21 Tract. Pain 10 Perfor. 1 (Surgery 3)	18 (33%)	7	0	11	6	0
Gastr.	1-3	8	51.0 (34-70)	Hemorrh. 1 Intr. Pain 3	Hemorrh. 1 Intr. Pain 3 Tract. Pain 3	2 (25%)	1	1	0	1	0
	+3	7	49.0 (31-63)	Hemorrh. 2 Perfor. 1 Intr. Pain 4 (Surgery 1)	Hemorrh. 3 Intr. Pain 4	2 (25%)	2	0	0	0	0
Margin.	+3	3	47.0 (34-56)	Hemorrh. 3 (Surgery 3)	Hemorrh. 3	2 (67%)	2	0	0	1	0
Clinical posit. but neg. x-ray	1-3	4	28.3 (25-32)	0 0	Tract. Pain 4	1 (25%)	0	0	1	0	0
	+3	4	44.3 (38-48)	Hemorrh. 2 Intr. Pain 2	Hemorrh. 2 Intr. Pain 1 Tract. Pain 1	1	1	0	0	0	0
Total		100	Av. 41.7	Hemorrh. 26 Perfor. 12 Intr. Pain 29 (Surgery 10)	Hemorrh. 39 Perfor. 1 Intr. Pain 35 Tract. Pain 25 (Surgery during hosp. 3) (Death dur. hosp. 1)	34%	14%	1%	19%	9%	2%

The control series of 100 patients treated with aluminum hydroxide preparations were divided into the same subgroups as the SCMC-MgO series (Table No. 3). There were 74 duodenal ulcers, of which 54 were classified as chronic; 15 gastric ulcers, with 7 considered chronic; 3 marginal ulcers; and 8 patients lacking radiographic confirmation of the clinical diagnosis. The duration of symptoms for the duodenal ulcer group was 9.3 years, with a range from one day to 31 years; the gastric lesions had an average duration of 5.2 years (two days to 29 years); and the marginal ulcers had an average of 15.3 years (3 to 28 years); the group, unconfirmed by X-ray, averaged 8.3 years (7 mos. to 27 years). Hemorrhage was the reason for admission in 37; perforation in 1; and 35 were classified as having intractable pain. Of the chronic duodenal ulcers, three required surgery for obstructive symptoms at the initial admission. After one year, 34% of the total were readmitted to the hospital, with hemorrhage in 14%, perforation in 1%, and intractable pain in 19%. Surgery was performed in 9% of the entire group, of which one was an acute gastric ulcer, which appeared malignant clinically, but histologically was benign. One patient with an acute duodenal ulcer, operated for gastro-intestinal hemorrhage during hospitalization, died.

Between 2 to 6 months after discharge from the hospital, 65% of 105 patients treated with SCMC-MgO were asymptomatic, against 49% of the control series. Of the SCMC-MgO group 28% were complaining of tractable pain, and only 7% had suffered recurrences, against 29% and 22% respectively in the control group. The difference between 7% and 22% appears to be significant. At 10 to 12 months, 61% of the SCMC-MgO group were still asymptomatic, 15% had tractable pain, and 24% had recurrences (Graph 1). It is interesting to note that the recurrence rate increased for both series in the second evaluation, but the percentage of patients who were asymptomatic with SCMC-MgO

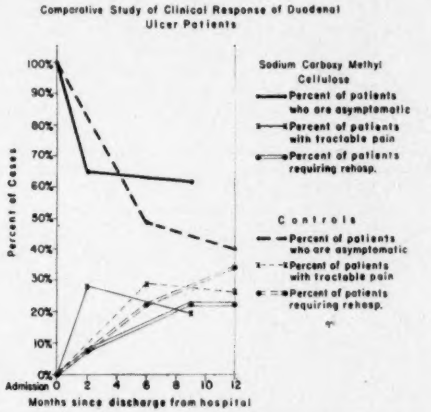
Graph 1



did not decrease much. Most of the recurrences occurred in the group classified as having tractable pain. This was not so in the control group, as most of the recurrences were among those who had been asymptomatic before.

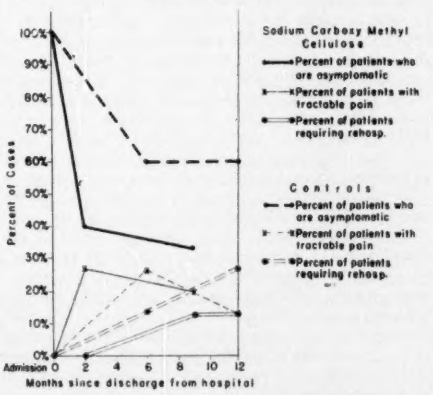
Patients with duodenal ulcer constituted the largest subgroups in both series. Of these, the SCMC-MgO group had 22% recurrences, against 32% for the controls (Graph 2). For the groups of gastric ulcers,

Graph 2



generally the SCMC-MgO group did better than the control group, although the control group showed more patients to be completely asymptomatic than the SCMC-MgO group (Graph 3). The recurrence rates, how-

Graph 3



ever, were lower for the latter group. Both groups were too small to consider the difference to be significant. Ten patients did not respond to SCMC-MgO medication during initial hospitalization; 7 of whom were eventually operated after further failure of other medications.

During the hospitalization of the 129 patients treated with SCMC-MgO, preference for medications was determined by questioning 107 patients. SCMC-MgO was preferred to aluminum hydroxide by 69% of the group, while 16% perferred the latter. Two patients (2%) preferred Sippy powders, and 13% had no particular preference. The main objection to the aluminum hydroxide preparations was constipation, and to the SCMC-MgO tablets it was the sensation of sticking in the esophagus when not followed by sufficient water.* Constipation of either a chronic nature or due to previous medication was noted in 41% of the 129 patients. Eighty-five per cent of these received immediate relief when put on SCMC-MgO.

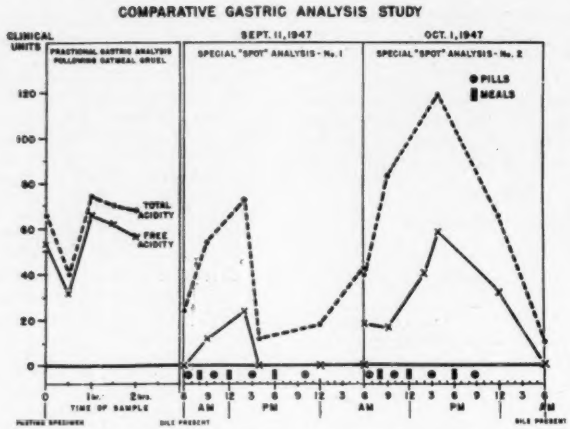
Despite the known inconsistencies in the evaluation of post-therapeutic gastric analysis (136), a repeat gastric analysis with histamine stimulation was done one to two months following discharge from the hospital on 48 patients of the SCMC-MgO group. During hospitalization, 10 patients had hyperacidity above 50° free acid, 22 ranged between 10° to 15°, and 16 patients had hypoacidity. The number of patients showing an elevation of their gastric acidity was 15, whereas only 9 showed a decrease. None had true anacidity, sustaining the view that peptic ulcers are never seen in that condition. The findings support also our experience, that gastric acidity may rise and stay up after an ulcer has healed.

An attempt was made to determine by spot gastric analysis technique, whether SCMC-MgO in the dosage and time intervals administered, maintained an adequate low acidity during the day, despite the stimulation of frequent meals (Graph 4). Thus, a patient with a long history of duodenal ulcer was selected, who tolerated gastric aspirations well. A control analysis following oatmeal gruel revealed a free acidity between 50 and 65°. He was then instructed to continue on his set regime of medications and Gastric 2 diet, and his stomach contents were aspirated between medications and meals: at 6 and 9 a.m., at 2 and 4 p.m., and at 12 a.m. The first examination revealed a peak of only 22° of free acid at 2 p. m., with 0° during the rest of the day. Before attempting larger series to corroborate these encouraging results, it was decided to recheck the same patients, in order to determine whether the results were consistent for the same individual. On the second examination, there was a marked afternoon rise to almost 50° of free acidity, differing markedly from the previous test. This inconsistency was noted by Forsgren (225) in 2/3rds of the patients studied after an Ewald meal at 8 a.m., noon, and 6 p.m.

Of the 129 patients of the SCMC-MgO series, only 88 took advantage of an opportunity to present themselves for a 3 months radiographic checkup. Activity was still noted in 29, either by enlargement of the crater or by continued irritability. Thirty-seven were declared inactive, and 23 were considered healed. Slight irregularity of the duodenal cap was noted in 2 of 9 patients previously found to be negative on roentgenologic examination. It is interesting to note that, al-

*These tablets must not be chewed, but swallowed with sufficient water, milk, or other liquid. In order to prevent as much as possible the sensation of sticking of the tablet in the esophagus, the size of the commercial tablet was cut into half later, and two tablets were recommended (Carmethose).

Graph 4



though 29 patients or 25.5% had x-ray evidence of activity, only 7% of the total group had a clinical recurrence at that time; 2% with hemorrhage and 5% with intractable pain. There were 31 patients who claimed tractable pain, but the majority of these failed to show radiographic evidence of ulcer activity. Several of the patients with roentgenologic evidence of ulcer activity claimed complete relief of ulcer distress with the SCMC-MgO medication. One of these patients, who had a history of duodenal ulcer of less than 3 years, revealed a persistent 100% gastric retention at 6 hours, but complained of no ill effects. He, at first, refused rehospitalization, but after one week returned voluntarily for treatment, although he claimed to be asymptomatic. After three weeks of aspirations and antispasmodics, no evidence of obstruction could be obtained, and he was again discharged. One year after that episode, the patient reported that he was still asymptomatic, but refused further radiographic study. This inconsistency between subjective complaints and radiologic study has been reported also by Hussar (72).

TREATMENT OF OUT-PATIENTS WITH SEVERE PAIN

Of the patients who developed severe symptoms during the active out-patient treatment phase with SCMC-MgO, 15 were put on a strict management with varying doses of combined tablets of SCMC-MgO with Trasentine. Each of these tablets contained 450 mgms. of sodium carboxymethylcellulose, 150 mgms. of magnesium oxide, and 75 mgms. of Trasentine. Trasentine was found to be useful in peptic ulcer otherwise refractory to diet, alkalies, sedation, and belladonna, by Spier et al (226). The basis of action, according to Goodman and Gilman (227) is its anodyne and local anesthetic effect on the gastroduodenal mucosa. Gold (228) has emphasized effective relaxation of the stomach by Trasentine in cases of pylorospasm and intractable ulcer pain.

The dose varied from one tablet four times a day, with or without maintenance dosage of SCMC-MgO tablets during the day, to one tablet every four hours. The duration of this treatment varied for each patient, according to his response, and ranged from 2 to 60 days. No toxic effects of the antispasmodic were noted. The reasons for this medication were: partial pyloric obstruction with recurrent vomiting, pain and retention in 7 patients; intractable pain in 7; and one patient with radiologic and aspiration evidence of almost 100% retention in 6 hours, but no subjective complaints. Twelve of these patients had histories of duodenal ulcers of more than three years duration; 2 had duodenal ulcers for less than 3 years; and only one had an acute gastric ulcer. The special medication was discontinued after 48 hours if the patient did not register some improvement, as it was felt that the symptoms and signs presented in most cases were serious enough to warrant re-hospitalization or even surgery. One patient continued to take the medication for 25 days before stating that he did not get any relief and was therefore rehospitalized.

Results indicate that 6 of these patients obtained immediate relief from their complaints and did not require rehospitalization during a period where plain SCMC-MgO failed to keep the patient comfortable. Four of these patients originally had intractable pain, while only two had signs of partial obstruction. Slight improvement, or complaints of transitory distress not requiring further hospitalization, was noted in 4 other patients. Prior to treatment, 2 of these had intractable pain and the other 2 had symptoms of partial obstruction. Four patients had no beneficial effect from the antispasmodic combination while ambulatory and were hospitalized. One of these was operated later for a gastric ulcer, a gastric resection and vagotomy being done. One patient, while in the hospital for partial obstruction and tarry stools, failed to respond to the medication. He was then treated with aspirations and Gelusil and responded slowly.

The combination of Trasentine with SCMC-MgO seems to be warranted in the treatment of otherwise intractable pain and partial pyloric obstruction. Of 14 ambulatory patients with symptoms warranting readmission to the hospital, only 4 were not benefitted sufficiently to be able to continue their daily routine as outpatients. One of these was admitted to the hospital and required surgery. It is felt that the dosage schedule should vary for each individual patient, with 1 tablet given four times a day as the minimum.

DISCUSSION

We have stressed before (236) the absolute need for uniformity in the study of recurrence rates in a problem as diversified as peptic ulcer. It is obvious that comparison between any two investigations is almost impossible, if each author has based his study on different criteria of recurrence as well as followups at various time intervals. In fact, several authors do not even mention how long the patient had been studied. A careful definition of the criteria for failure must be based on tangible evidence of recurrent ulceration or symptoms reasonably ascribed to the ulcer. Unfortunately, such findings as radiographic improvement and repeat gastric analysis are not definitive enough to be valid. The mere existence of tractable pain incriminates the lack of cooperation of the patient more than it does the investigated medication. Each patient must be followed for the same period of time, and this should be identical with a comparable group of controls. The final criteria of efficacy for any therapeutic agent for peptic ulcer should be the rapidity of time in which the patient has become asymptomatic, and the length of time he could be maintained asymptomatic. Accomplishing the first factor has been relatively easy on any therapy, but the latter goal has not been adequately reached by any medication since Cruveilhier's time (1) and probably before. In our study, the control series and the SCMC-MgO series were followed for one full year. A patient with one or more recurrences in a single year was considered a failure, even if he failed to return for study in the interval between recurrences.

An attempt was made by Batterman (97) to compare statistically various frequently used antacids. He defined a therapeutic ratio as the percentage of patients asymptomatic after about 6 weeks of therapy, divided by the percentage of patients constipated. This in our opinion is not a good method, for the ratio will depend more on the degree of constipation in the individual series, than on the effectiveness of the medication as an antacid. A fair percentage of patients with peptic ulcer may be constipated from causes other than the ulcer or the medication. Nonetheless, we feel that this method presents at least one approach to comparison. Batterman's best ratio was obtained with the use of Gelusil modified with magnesium trisilicate, and was reported as 14.87 for the tablets and 7.00 for the liquid. The tablet preparation of SCMC-MgO was second best, presenting a ratio of 5.5 for the early effects as studied by Batterman, and a ratio of 4.0 after one year. The ratios for Amphojel, Creamalin, Phosphagel and Amphojel with homatropine methylbromide varied between 2.31 and 4.03 (97).

Clinically, after a one year evaluation, it was felt that the combination of sodium carboxymethylcellulose, 450 mgms, and magnesium oxide, 150 mgms offer a preparation that was slightly more effective than aluminum hydroxide preparations on our type of patient material in the symptomatic treatment of peptic ulcer. The relatively small dose of magnesium was considered and proved to be safe from the standpoint of irritation to the intestinal mucosa. Only 5 of 129 patients had diarrhea while on medication, but since this was of short duration and not severe, and since it disappeared while medication with SCMC-MgO was continued, it was felt that it was not due to the magnesium. The subjective advantage of this preparation was manifested in the personal preference of the patients treated, who claimed rapid relief from distress, ease of administration, and adequate laxation. Objectively, the comparison of recurrence rate of the controls, 34%, and of the SCMC-MgO series, 23.8%, may not mean a significant difference. The investigated patients were given a more thorough course of instruction in methods of preventing recurrences and were allowed to lean on the investigator for moral support during emotionally trying periods. This was not done as effectively in the control group. However, when compared to the results of the summary of the literature on recurrence rates for medical therapy (236), both the present control series as well as the SCMC-MgO series show significantly lower recurrence rates than the 42% recurrence rates of immediate to 2 year studies, accumulated by us from the literature (235-6). This difference may be due to the rather stringent requirements for classification of recurrence in the present study.

Only 41 of 129 patients gave a definite history of developing their first ulcer distress prior to the armed service; and of these, 15 patients (37%) were given medical discharges. These figures more closely approach the findings of Hussar (72), 33% with preinduction digestive symptoms than those reported by other investigators, 81%, or as high as 90% (59). This tends to indicate that our material was also influenced by the compensation factor described by Hussar (72).

The combination of 75 mgms. of Trasentine with the sodium carboxymethylcellulose-magnesium oxide tablets, when used for severe symptoms such as partial pyloric obstruction and otherwise intractable pain, was able to benefit all but 4 of 14 patients to a sufficient degree to enable them to continue as out-patients.

The use of SCMC-MgO tablets prophylactically, to prevent recurrent hemorrhage in the spring and fall, was effectively carried out on a 25-year-old white male who had suffered severe gastro-intestinal hemorrhages from a duodenal lesion, requiring hospitalization and transfusions in 2 preceding seasons. He has now passed through three critical seasonal periods with no recurrence. Another patient with a history of epigastric distress for 7 years was found to have a definite gastric ulcer by radiographic study. He was treated with SCMC-MgO, and after 7 weeks a repeat film was reported as being negative. He remained asymptomatic for only 3 months on this management, and another roentgenologic study revealed the recurrence of a small ulcer crater. He was then placed on an aluminum hydroxide preparation, and considered a failure for SCMC-MgO. A routine gastro-intestinal series was repeated in another 8 months, and the ulcer was still present. He was then restarted on the regular SCMC-MgO management, and the radiologic evidence of the lesion was completely absent in 3 months. He remained subjectively asymptomatic on both types of treatment, but preferred to take the SCMC-MgO tablets because of relief of chronic constipation.

A commercial preparation of SCMC-MgO tablets without and with Trasentine, and of liquid SCMC, has become available under the trade name of Carmethose.* The tablets are half the size of those used in the above work, containing each 225 mg of SCMC and 75 mg of

*Supplied by The Ciba Pharmaceutical Products, Inc., Summit, N. J.

MgO. Clinical tests with these tablets showed them to be equally effective in the ulcer patient as the larger experimental tablets used in the clinical work reported above.

CONCLUSIONS AND SUMMARY

In conclusion, we feel that the new synthetic preparation of SCMC-MgO presents a valuable addition to the armamentarium for the treatment of peptic ulcer. There is not any one drug or method known which will be equally effective in every ulcer patient. One has to individualize in the therapy, and one has to find to which drug each patient responds best. We feel that the new preparation ranks among the best of the group of drugs available for ulcer therapy, and that it deserves a wide trial and critical follow-up. Theoretically, in laboratory experiments, and practically, in clinical use, it has shown to be promising.

1. A preparation of sodium carboxymethylcellulose, 450 mgms, and magnesium oxide, 150 mgms was found to be slightly more effective than aluminum hydroxide preparations on a comparative group of veterans studied for recurrences during a one year survey.

2. A method of evaluating clinically the efficacy of any new preparation for peptic ulcer treatment by study of the recurrence rates has been discussed. The need for definite criteria and duration of study has been emphasized.

3. The recurrence rate for the experimental group treated with SCMC-MgO was 23.8% as compared to 34% for a comparable control group, and 42% found by summarizing the literature from 1899 to 1948 for recurrence rates on medical management.

4. The use of Trasentine, 75 mgms, with the SCMC-MgO was found to be an effective way to control otherwise intractable spasm and pain.

5. SCMC-MgO was also found to be an effective bulk laxative, relieving 85% of constipated ulcer patients.

6. SCMC-MgO has become available commercially in a smaller tablet containing half the quantity of both drugs used in the above work under the trade name of Carmethose.

BIBLIOGRAPHY

Of the present and of the 4 preceding papers

1. Cruveilhier, J.: Anatomie Pathologique du Corps Humain au Description avec Figures Lithographiees et Coloriees des Diverses Alterations Morbides dont Le Corp Humain est Susceptible. Vol. 1, Bailliere. Paris, 1829.
2. Sippy, B. W.: J. A. M. A., 6:1625, 1915.
3. Granet, E.: Rev. of Gastroent., 7:25, 1948.
4. Editorial: Gastroenterology, 6:216, 1946.
5. Ingelfinger, F. J., and Moss, R. E.: Med. Clin. N. Amer., Sept., 1945, p. 1162.
6. Palmer, W. L.: Editorial, Am. Jour. of Med., 5:470, 1948.
7. Crohn, B. B.: Frank H. Lahey Birthday Volume, p. 137, Charles C. Thomas, Baltimore, 1940.
8. Nielsen, N. A.: Acta med. Scand., 58:1, 1923.
9. St. John, F. B., and Flood, C. A.: Ann. of Surg., 110:37, 1939.
10. Chaiken, N. W.: Rev. of Gastroent., 14:49, 1947.
11. Drossner, J. L., and Miller, T. G.: Am. J. Med. Sci., 199:90, 1940.
12. Emery, E. S., and Monroe, R. T.: Arch. Int. Med., 55:271, 1935.
13. Raimondi, P. J., and Collen, M. F.: Gastroenterology, 6:176, 1946.
14. Flood, C. A.: Gastroenterology, 10:184, 1947.
15. Boles, R. S.: J. A. M. A., 136:528, 1948.
16. Cohnheim, P.: Diseases of the Digestive Canal, p. 116, J. P. Lippincott Co., Phila., 1914.
17. Eggleston, E. L.: Trans. Amer. Gastro-Entero. Assoc., 71, 1926.
18. Moynihan, B.: Duodenal Ulcer, W. B. Saunders Co., 2nd ed., p. 113, Phila., 1912.
19. Necheles, H.: Gastroenterology, 7:622, 1946.
20. Cowgill, G. R.: Macleod's Physiology in Modern Medicine, C. V. Mosby Co., p. 911, St. Louis, 1941.
21. Berger, S. S.: Rev. of Gastroent., 14:117, 1947.
22. Schwartz, K.: Beitr. z. Klin. Chir., 67:96, 1910.
23. Winkelstein, A., Cornell, A., and Hollander, F.: Surgery, 17:096, 1945.
24. Jordan, S. M.: Gastroenterology, 9:237, 1947.
25. Boles, R. S., Riggs, H. E., and Griffith, J. O.: Am. J. Digest. Dis., 6:632, 1939.
26. Necheles, H.: Am. J. Digest. Dis., 4:643, 1937; 6:635, 1939.
27. Bachrach, W. H., Grossman, M. I., and Ivy, A. C.: Gastroenterology, 6:356, 1946.
28. Bachrach, W. H., Grossman, M. I., and Ivy, A. C.: Gastroenterology, 6:563, 1946.
29. Wolf, S., and Wolff, H.: Human Gastric Function, Oxford University Press, New York, 1943.
30. Aycock, B., and Hendrick, W.: J. A. M. A., 133:1258, 1947.
31. Tinney, W. S., Hall, B. H., and Griffin, H. Z.: Proc. Staff Meet. Mayo Clinic, 18:24, 1943.
32. DeBusscher, G.: Gastroenterologia, 72:154: 1947.
33. Kirstenson, A.: Acta med. Scand., 120:31, 1946.
34. Guilfoil, J. A.: Calif. and West. Med., 29:15, 1928.
35. Maingot, R.: Abdominal Operations, D. Appleton-Century Co., Inc., Vol. 1, p. 179, New York, 1940.
36. Tidy, H.: Gastroenterologia, 72:241, 1947.
37. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, Oxford Medical Publications, p. 29, London, 1929.
38. Hollander, F.: Surg. Clinics of N. Amer., 27:265, 1947.
39. Lahey, F. H.: J. A. M. A., 136:534, 1948.
40. Smith, F. H., and Jordan, S. M.: Gastroenterology, 11:575, 1948.
41. Mulsow, F. W.: Am. J. Digest. Dis., 8:112, 1941.
42. Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J.: Arch. Int. Med., 49:345, 1932.
43. Kiefer, E. D., and McKell, D. M.: J. A. M. A., 133:1055, 1947.
44. Boles, R. S., and Dunbar, W.: Geriatrics, 1:217, 1946.
45. Rafsky, H. A., Weingarten, M., and Krieger, C. L.: J. A. M. A., 136:739, 1948.
46. Meyer, J., and Saphir, O.: Am. J. Digest. Dis., 10:28, 1943.
47. Bolen, H. L.: Rev. of Gastroent. 13:229, 1946.
48. Jones, A. A.: New York Med. Jour., 61:76, 1895.
49. Jordan, S. M., and Kiefer, E. D.: Am. J. Surg., 15:472, 1932.
50. Jaffe, R. H., and Laing, D. R.: Arch. Int. Med., 53:851, 1934.
51. Walsh, B. J., Bland, E. F., Taquini, A. C., and White, P. D.: Am. Heart Jour., 21:689, 1941.
52. Sandweiss, D. J.: Gastroenterology, 9:335, 1947.
53. Office of Selective Service Records: quoted from Sandweiss, 52.
54. Rowntree, L. G.: Psychosom. Med. 7:27, 1945.
55. Willcox, P. H.: Brit. Med. Journ., 1:1008, 1940.
56. Tidy, H.: Brit. Med. Jour., 2:473, 1943.
57. Stewart, B. D. W., and Winsen, D. H. deR.: Lancet, 1:259, 1942.
58. Kantor, J. L.: J. A. M. A., 120:254, 1942.
59. Zetzel, L.: Gastroenterology, 3:472, 1944.
60. Chamberlin, D. T., and Wallace, W. C.: Mil. Surgeon, 92:193, 1943.
61. Mahlo: quoted from Schindler, R.: War Med., 2:263, 1942.
62. Berk, J. E.: Gastroenterology, 3:464, 1944.
63. Dunn, W. H.: War Med., 2:167, 1942.
64. Kirk, R. C.: Am. J. Digest. Dis., 10:411, 1943.
65. Flood, C. A.: War Med., 3:160, 1943.
66. Berk, J. E., and Frediani, A. W.: Gastroenterology, 3:435, 1944.
67. Urquehart, R. W. I., Singleton, A. C., and Feasby, W. R.: Canad. Med. Jour., 45:391, 1941.
68. Gainsborough, H., and Slater, E.: Brit. Med. Jour., 2:253, 1946.
69. Kirk, R. C.: Gastroenterology, 7:168, 1946.
70. Wilen, C. J. W., and Poole, P. P.: Gastroenterology, 9:253, 1947.
71. Halsted, J. A., and Weinberg, H.: Med Bull. of the Medit. Theater of Oper., 1:2, 1944.
72. Hussar, A. E.: Gastroenterology, 11:183, 1948.
73. Adams, W. L.: Arch. Int. Med., 63:1030, 1939.
74. Dick, G. P., and Eisele, C. W.: J. A. M. A., 118:38, 1942.
75. Kraemer, M.: Am. J. Digest. Dis., 8:56, 1941.
76. Fogelson, S. J.: J. A. M. A., 96:673, 1931.
77. Hardt, L. J., and Rivers, A. B.: Arch. Int. Med., 31:171, 1923.
78. Oakley, W.: Lancet, 2:187, 1935.
79. Hubble, D.: Lancet, 2:634, 1935.
80. Eisele, C. W.: Arch. Int. Med., 63:1048, 1939.
81. Eisele, C. W.: J. A. M. A., 114:2363, 1940.
82. Crohn, B. B., and Reiss, J.: Am. J. Med. Sci., 159:70, 1920.
83. Wosika, P. H., and Emery, E. S.: Ann. Int. Med., 9:1070, 1935.
84. Wilkinson, S. A., and Commandura, P. D.: New Eng. J. Med., 223:972, 1940.
85. Brown, C. F. G., and Dolkart, R. E.: J. A. M. A., 113:276, 1939.
86. Clark, B. B., and Adams, W. L.: Gastroenterology, 9:284, 1947.
87. Breuhaus, H. C., and Eyerly, J. B.: Ann. Int. Med., 14:2285, 1941.
88. Gershon-Cohen, J.: Radiology, 48:232, 1947.
89. Freezer, C. R. E., Gibson, C. S., and Matthew, E.: Guy's Hosp. Reports, 8:191, 1928.
90. Kraemer, M.: Am. J. Digest. Dis., 8:56, 1941.
91. Kirsner, J. B., and Palmer, W. L.: Am. J. Digest. Dis., 7:85, 1940.
92. Kirsner, J. B.: Am. J. Digest. Dis., 8:53, 1941.
93. Crohn, B. B.: J. Lab. and Clin. Med., 14:610, 1929.
94. Ivy, A. C., Terry, L., Pauley, G. B., and Bradley, W. B.: Am. J. Digest. Dis., 3:879, 1937.
95. Boyd, L. H., Russ, W. R., and Barowsky, H.: Rev. of Gastroent., 9:20, 1942.
96. Havens, W. P.: J. A. M. A., 113: 1564, 1939.
97. Batterman, R. C., and Ehrenfeld, I.: Gastroenterology, 9:141, 1947.
98. Jonkelson, I. R.: Am. J. Digest. Dis., 14:11, 1947.
99. Child, G. P., and Aurbach, S. H.: Am. J. Digest. Dis., 14:63, 1947.
100. Monaghan, J. F.: quoted from Bockus, H.: Gastroenterology, Vol. 1, p. 455, W. B. Saunders Co., Phila., 1944.
101. Bockus, H.: Gastroenterology, Vol. 1, W. B. Saunders Co., p. 455, Phila., 1944.
102. Fauley, G. B., Ivy, A. C. Terry, L., and Bradley W. B.: Am. J. Digest. Dis. 5:792, 1939.
103. Ehrmann, R.: Am. J. Digest. Dis., 12:154, 1945.
104. Grondahl, R. D., and West, E. S.: Am. J. Digest. Dis., 12:197, 1945.
105. Lichstein, J., Simpkins, S., and Bernstein, M.: Am. J. Digest. Dis., 12:65, 1945.
106. Beazell, J. M., Schmidt, C. R., and Ivy, A. C.: Am. J. Digest. Dis., 5:164, 1939.
107. Schiffrin, M. J., and Komarov, S. A.: Am. J. Digest. Dis., 8:215, 1940.
108. Hoffman, W. S., and Dyniewicz, H. A.: Gastroenterology, 5:512, 1945.
109. Whitcomb, B. B.: J. of Conn. Med. Soc., 3:272, 1939.
110. Woldman, E. E.: Am. J. Digest. Dis., 8:39, 1941.
111. Kirsner, J. B.: Am. J. Digest. Dis., 8:160, 1941.
112. Fliegelman, M. T., Panzer, L. M., and Rhoads, J. E.: Surgery, 10:387, 1941.
113. Woldman, E. E., and Polan, C. G.: Am. J. Med. Sci., 198:155, 1939.

114. Spellberg, M. A., and Keeton, R. W.: Arch. Int. Med., 63:1095, 1939.
115. Krieder, H. R.: J. A. M. A., 117:1354, 1941.
116. Rossett, N. E., and Flexner, J.: Ann. Int. Med., 18:193, 1943.
117. Babkin, B. P.: Secretory Mechanism of the Digestive Glands; Paul B. Hoeber, Inc., p. 173, New York, 1944.
118. Mecray, P. M., Barden, R. P., and Ravdin, I. S.: Surgery, 1:53, 1937.
119. Hoelzel, F., and DaCosta, E.: Am. J. Digest. Dis., 4:325, 1937.
120. Matzner, M. J., Windmer, C., and Sobel, A. E.: Am. J. Digest. Dis., 5:36, 1938.
121. Riggs, H. E., Reinhold, J. G., Boles, R. S., and Shore, P. S.: Am. J. Digest. Dis., 8:383, 1941.
122. Levy, J. S.: Gastroenterology, 4:375, 1945.
123. Kenamore, B., Lonegan, W., and Shy, J. C.: Gastroenterology, 10:177, 1948.
124. CoTui, Wright, A. M., Mulholland, J. H., Galvin, T., Barcham, L., and Garst, G. R.: Gastroenterology, 5:5, 1945.
125. CoTui, Wright, A. M.: Bull. New York Acad. Med., 21:629, 1945.
126. Mulholland, J. H., CoTui, Wright, A. M., Vinci, V. J., and Shafiroff, B.: Ann. Surg., 118:1015, 1943.
127. Ruggiero, W. F., CoTui, Wright, A. M., and Bianco, A. A.: N. Y. State J. Med., 46:2395, 1946.
128. Kantor, J. L.: Discussion of paper by Ruggiero.
129. Rossien, A. X.: Am. J. Digest. Dis., 14:205, 1947.
130. Woldman, E. E., Fishman, D., Knowlton, R. S., Rousuck, A. A., and Stoner, W. C.: J. A. M. A., 137:1289, 1948.
131. Thomas, J. E., and Crider, J. O.: Am. J. Physiol., 126:28, 1939.
132. Hedges, H. H.: Gastroenterology, 8:476, 1947.
133. Heidenhain, R.: quoted from Hermann, L.: Handbuch der Physiologie, Vol. 5, p. 122, F. C. W. Vogel, Leipzig, 1883.
134. Pavlov, I. P.: The Work of the Digestive Glands, C. Griffith, Co., London, 1910.
135. Zweig, W.: Arch. f. Verdauungskr., 12:364, 1906.
136. Webster, D. R.: Am. J. Physiol., 90:718, 1929.
137. Bolton, C., and Goodhart, G. W.: J. Physiol., 73:115, 1931; 77: 287, 1933.
138. Kim, M. L., and Ivy, A. C.: J. A. M. A., 97:1511, 1931.
139. Babkin, B. P., and Komarov, S. A.: Canad. J. Med. Ass., 27:463, 1932.
140. Ivy, A. C., and Oyama, Y.: Am. J. Physiol., 57:51, 1921.
141. Lim, R. K. S.: Am. J. Physiol., 69:318, 1924.
142. Necheles, H., and Coyne, A.: Arch. Int. Med., 55:395, 1935.
143. Hurst, A.: quoted from Fogelson (149).
144. Whitlow, J. F.: quoted from Fogelson (149).
145. Brestkin, M. P., and Bykov, K. M.: J. Russe Physiol. 7:301, 1924.
146. Mahlo, A.: Der Magenschleim, Ferd. Enke, Stuttgart, 1938.
147. Rivers, A. B., Vanzant, F. R., and Essex, H. E.: J. A. M. A., 98: 1156, 1932.
148. Brown, C. F. G., Cromer, S. P., Jenkinson, E. L., and Gilbert, N. C.: J. A. M. A., 99:98, 1932.
149. Fogelson, S. J.: Arch. Int. Med., 55:7, 1935.
150. Meyer, J., Seidmon, E. E., and Necheles, H.: Ill. Med. Jour., 6:339, 1933.
151. Mathieu, A.: Jour. de Med. de Paris, 2:23, 1911.
152. Jones, K. K., Ivy, A. C., and Atkinson, A. J.: Ill. Med. Jour., 63:377, 1933.
153. Hardt, L. L., and Brody, L. P.: Arch. Surg., 55:584, 1947.
154. Kammerling, E. M., and Steigmann, F.: Am. J. Digest. Dis., 14: 381, 1947.
155. Shay, H., Komarov, S. A., Siplet, H., and Gruenstein, M.: Am. J. Digest. Dis., 14:99, 1947.
156. Schoch, D., and Fogelson, S. J.: Proc. Soc. Exper. Biol. and Med., 50:304, 1942.
157. Kirsner, J. B., and Wolff, R. H.: Proc. Soc. Exper. Biol. and Med., 54:11, 1943.
158. Steigmann, F., and Marks, A. R.: Proc. Soc. Exper. Biol. and Med., 54:25, 1943.
159. Steigmann, F., and Marks, A. R.: Am. J. Digest. Dis., 11:173, 1944.
160. Adams, R. A., and Hawkins, R. L.: J. Soc. Chem. Ind., 54:1, 1935.
161. Segal, H. L., Hodge, H. C., Watson, J. S., and Scott, W. J. M.: Gastroenterology, 4:484, 1945.
162. Segal, H. L., Hodge, H. C., Watson, J. S., and Coates, H.: Gastroenterology, 8:198, 1947.
163. Kraemer, M., and Lehman, D.: Gastroenterology, 8:202, 1947.
164. Martin, G. J., and Wilkinson, J.: Gastroenterology, 6:315, 1946.
165. Spears, M. M., and Pfeiffer, M. J.: Gastroenterology, 8:191, 1947.
166. Kosaka, T., and Lim, R. K. S.: Proc. Soc. Exper. Biol. and Med., 27:890, 1930.
167. Ivy, A. C.: Federation Proc., 4, 222, 1945.
168. Sharpey-Schafer, Sir B.: The Endocrine Organs, 2nd Ed., Part 1, Longmans, Green and Co., London, 1924.
169. Gray, I. S., Bradley, W. B., and Ivy, A. C.: Am. J. Physiol. 118, 463, 1937.
170. Hands, A. P., Greengard, H., Preston, F. W., Fauley, G. B., and Ivy, A. C.: Endocrinology, 30:905, 1942.
171. Morris, C. R., Grossman, M. I., and Ivy, A. C.: Am. J. Physiol., 148:382, 1947.
172. Pauls, F. A., Wick, A. N., and McKay, E. M.: Science, 103:673, 1946.
173. Greengrad, H., Atkinson, A. J., Grossman, M. I., and Ivy, A. C.: Gastroenterology, 7:625, 1946.
174. Kirsner, J. B., Levin, E., and Palmer, W. L.: Gastroenterology, 10, 256, 1947.
175. Sandweiss, D. J., Sugarman, M. H., and Lockwood, B. C.: J. A. M. A., 138:552, 1948.
176. Code, C. F., and Varco, R. L.: Proc. Soc. Exper. Biol. and Med., 44:275, 1940.
177. Scheinberg, S., Bralow, S. P., and Necheles, H.: Surgery, 24, 972, 1948.
178. Shelanski, H. A., and Clark, A. M.: Food Research, 13:29, 1948.
179. Brown, C. J., and Houghton, A. A.: J. Soc. Chem. Ind., 60:254, 1941.
180. Rowe, V. K., Spencer, H. C., Adams, E. M., and Irish, D. D.: Food Research, 9:175, 1944.
181. Werle, E.: Chem. Abstracts, 37:2807, 1943.
182. Fittipoldi, J., and Davis, P. L.: Gastroenterology, 10:667, 1948.
183. Gray, H., and Tainter, M. L.: Am. J. Digest. Dis., 8:130, 1941.
184. Stein, D., and Gelehrter, J.: Rev. of Gastroent. 7:39, 1940.
185. Ivy, A. C., and Isaacs, B. L.: Am. J. Digest. Dis., 5:315, 1938.
186. Block, L. H.: Am. J. Digest. Dis., 14:64, 1947.
187. Editorial: J. A. M. A., 137:992, 1945.
188. Tainter, M. L.: Proc. Soc. Exper. Biol. and Med., 54:77, 1943.
189. Mann, A. E.: Med. World, 59:592, 1941.
190. Blake, A. D.: Am. J. Digest. Dis., 15:336, 1948.
191. Blythe, R. H., Culesich, J. J., and Tuthill, H. L.: read at the A. A. A. S. C. meeting, Dec. 27, 1947, Chicago.
192. Rossien, A. X., and Victor, A. W.: Am. J. Digest. Dis., 14:226, 1947.
193. Bibliography for the Summary of Recurrence Rates in the Literature:
    1. Bamberger: Die innere u. die chirurg. Bhdl. d. [illegible]on. Magenbeschw. und ihre Erfolge, Berlin, 1909; quoted from Nielsen.
    2. Bernstein, B. M.: Rev. of Gastroent., 14:129, 1947.
    3. Blackfort, J. M., and Bowers, J. M.: Am. J. Med. Sci., 177:51, 1929.
    4. Brown, R. C.: J. A. M. A., 95:1144, 1930.
    5. Chaiken, N. W.: Rev. of Gastroent., 14:49, 1947.
    6. Clemmeson: quoted from Krarup.
    7. Cunha, F.: Am. J. Surg., 23:219, 1934.
    8. Deimasure: Enquete sur les resultats eoignes du traitment medical del'ulcere de l'estomac, Paris, p. 39, 1909.
    9. Douglas, D. M.: Gastroenterologia, 72:10, 1947.
    10. Drossner, J. L., and Miller, T. G.: Am. J. Med. Sci., 199:90, 1940.
    11. Dwyer, M. F., Blackford, J. M., Cole, W. S., and Williams, R. H.: Radiol., 36:217, 1941.
    12. Emery, E. S., and Menree, R. T.: Arch. Int. Med., 55:271, 1935.
    13. Easterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, p. 290, W. B. Saunders Co., Phila., 1936.
    14. Faulhaber: Muench. med. Wochenschr., 1913, N. O. 17; quoted from Nielsen.
    15. Fremont-Smith, M., and McIver, M. A.: Am. J. Med. Sci., 177:33, 1929.
    16. Flood, C. A.: Gastroenterology, 10:184, 1947.
    17. Forsyth, D.: Brit. Med. Jour., 1:780, 1924.
    18. Friedenwald, J.: Am. J. Med. Science, Aug., 1912.
    19. Friedenwald and Morrison: quoted from Hussar.
    20. Gainsborough, H., and Slater, E.: Brit. Med. Jour., 2:253, 1947.
    21. Glaessner, K.: Rev. of Gastroent. 1:136, 1934.
    22. Granet, E.: Rev. of Gastroent., 7:25, 1948.
    23. Greengard, H., Atkinson, A. J., Grossman, M. I., and Ivy, A. C.: Gastroenterology, 7:625, 1946.
    24. Greenough, R. B., and Joslin, E. P.: Am. J. Med. Sci., 118:167, 1899.
    25. Heuer, G. J.: The Treatment of Peptic Ulcer, J. B. Lippincott Co., Phila., 1944.
    26. Hewes: J. A. M. A., p. 838, 1906; quoted from Nielsen.
    27. Hufford, A. R.: Minn Med., 16:310, 1933.
    28. Hussar, A. E.: Gastroenterology, 11:183, 1948.
    29. Jordan, S. M., and Kiefer, E. D.: Am. J. Surg., 15:472, 1932.
    30. Kahrs, T., and Schrumpf, A.: Rev. of Gastroent., 14:673, 1947.
    31. Kemp, R. C.: Diseases of the Stomach, Intestines and Pancreas, 3rd Ed., W. B. Saunders Co., Phila., 1917, p. 295.
    32. Krarup, N. B.: Acta Med. Scand., 126:34, 1946.
    33. Martin, K. A.: J. A. M. A., 106:1468, 1936.
    34. Matisson, K.: Das Magengeschwuer, Berlin, 1931.
    35. Meyer and Kartoon: quoted from Granet.
    36. Moullin, M.: Brit. Med. Jour., p. 25, April, 1903; quoted from Nielsen.
    37. Natvig, P., Romoke, O., and Svaar-Seljessacter, O.: Acta Med. Scand., 113:444, 1943.
    38. Nielsen, N. A.: Acta Med. Scand., 58:1, 1923.
    39. Olpp, A. E.: Med. Records, 140:472, 1934.
    40. Paterson: Lancet, 10:1904; quoted from Nielsen.
    41. Pribram, B. O.: Presse med., 412:1453, 1933.
    42. Quigstad, I., and Romcke, O.: Acta med. Scand., 126:34, 1946.
    43. Raimondi, P. J., and Collen, M. F.: Gastroenterology, 6:176, 1946.
    44. Russell: Lancet, 10:1904; quoted from Nielsen.
    45. Sandweiss, D. J.: J. A. M. A., 106:1452, 1936.
    46. Sandweiss, D. J., and Myers, S. G.: Am. J. Digest. Dis., 1:338, 1934.
    47. Sandweiss, D. J., Saltzstein, H. C., and Glazer, W. S.: J. A. M. A., 108:700, 1937.
    48. Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., Saltzstein, H. C., and Farbman, A. A.: Am. J. Digest. Dis., 8:371, 1941.
    49. Sandweiss, D. J., Sugarman, M. H., and Lockwood, B. C.: J. A. M. A., 138:552, 1948.
    50. Schultz: Mitteilunnged a. d. Grenzgebiete Bd. 11, 1903; quoted from Nielsen.
    51. Smith, F. H., and Jordan, S. M.: Gastroenterology, 11:575, 1948.
    52. Smithies, F.: J. A. M. A., 85:674, 1925.
    53. Stowell: quoted from Kemp.
    54. St. John, F. B., and Flood, C. A.: Ann. Surg., 110:37, 1939.
    55. Vanzant, R.: quoted from Granet.
    56. Volini and McLaughlin: quoted from Granet.
    57. Wagner: Muench. med. Wochenschrift, Jan. 1904; quoted from Nielsen.
    58. Walton, A. J.: Brit. Med. Journ., 2:784, 1928.
    59. Wanke, R.: Deutsche Ztschr. f. Chir., 220:263, 1929.
    60. Weiss, A. G., and Aron, E.: Presse med., 41:1880, 1933.
    61. White: quoted from Emery and Balfour.
    62. Wolff: Volkmanns Sammlung klin. Vortr. N. O., 572, 1910; quoted from Nielsen.
194. Hollander, F., and Mage, S.: Surg., Gynec., and Obst., 76:533, 1943.
195. Jones, F. A.: Brit. Med. Jour., 2:441, 1947.
196. Aaron, A. H., Lipp, W. F., and Milch, E.: J. A. M. A., 139:514, 1949.
197. Krarup, N. B.: Acta med. Scand., 123:181, 1946.
198. Illingworth, C. F. W., Scott, L. D. W., and Jamieson, R. A.: Brit. Med. Jour., 2:787, 1946.
199. Matisson, K.: Das Magengeschwuer, Berlin, 1931.
200. Natvig, P., Romcke, O., and Svaar-Seljaesceter, O.: Acta med. Scand. 113:444, 1943.
201. Wirsung, E.: Arch. f. Verdauungskr., 11:197, 1905.
202. Conybeare, J. J.: Lancet, 2:1017, 1935.

203. Brown, R. C.: J. A. M. A., 95:1144, 1930.
204. Dwyer, M. F., Blackford, J. M., Cole, W. S., and Williams, R. H.: Radiol., 36:217, 1941.
205. Galambos, A.: Arch. Int. Med., 38:654, 1926.
206. Hellebrandt, F. A., Tepper, R. H., Grant, H., and Catherwood, R.: Am. J. Digest. Dis., 3:477, 1936.
207. Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J.: Arch. Int. Med., 49:345, 1932.
208. Klumpp, T. G., and Bowie, M. A.: J. Clin. Investig., 21:1, 1933.
209. Chency, G., and Bloomfield, A. L.: J. Clin. Investig., 5:511, 1928.
210. Palmer, W. L., and Nutter, P. B.: Arch. Int. Med., 65:499, 1940.
211. Vanzant, F. R., Berkson, J., Alvarez, W. C., and Eusterman, G. B.: Arch. Int. Med., 52:616, 1933.
212. Bloomfield, A. L., and Polland, W. S.: Gastric Anacidity, The MacMullin Co., p. 53, 1933, New York.
213. Ruffin J. M., and Dick, M.: Ann. Int. Med., 12:1940, 1939.
214. Abramson, L.: Acta med. Scand., 77:77, 1931.
215. Vanzant, F. R., Osterberg, A. E., Alvarez, W. C., and Rivers, A. B.: J. Clin. Invest., 12:557, 1933.
216. Bloomfield, A. L., Chen, C. K., and French, L. R.: J. Clin. Investig., 10:863, 1940.
217. Hurst, A. F.: Guy's Hosp. Reports, 79:249, 1929.
218. Meyer, J., Maskin, M., and Necheles, H.: Am. J. Digest. Dis., 3:474, 1936.
219. Bockus, H. L., Glassmire, C., and Bank, J.: Am. J. Surg., 12:6, 1931.
220. Brown, C. F. G., and Dolkart, R. E.: Arch. Int. Med., 60:680, 1937.
221. Voegtlin, W. L.: Gastroenterology, 9:125, 1947.
222. Emery, E. S., and Monroe, R. T.: Am. J. Roentgen., and Rad. Therapy, 25:144, 1931.
223. Akerlund, A.: Am. J. Surgery, 12:233, 1931.
224. Cummins, G. M., Grossman, M. I., and Ivy, A. C.: Gastroenterology, 7:20, 1946
225. Forsgren, E.: Acta med. Scand., 128:281, 1947.
226. Spier, E., Neuwelt, F., and Necheles, H.: Am. J. Digest. Dis., 6:387, 1939.
227. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, MacMillan Co., 1941, p. 479, New York.
228. Gold, H.: New York State J. Med., 15:2085, 1948.
229. Crohn, B. B. and Reiss, J.: Am. J. Med. Sci., 154:857, 1917.
230. Hamburger, W. W.: Deutsch. Arch. fuer klin. Med., 97:49, 1909.
231. Necheles, H., and Bralow, S. P.: unpublished data.
232. Brummer, P.: Acta med. Scand., 126:384, 1946.
233. Bloch, L., and Rosenberg, D. H.: Am. J. Med. Sci., 185:1, 1933.
234. Bralow, S. P., Spellberg, M. A., Kroll, H. and Necheles, H. Part I. Am. J. Dig. Dis., 17:41, 1950.
235. Bralow, S. P., Spellberg, M. A., Kroll, H. and Necheles, H. Part II. Am. J. Dig. Dis., 17:86, 1950.
236. Bralow, S. P., Spellberg, M. A., Kroll, H. and Necheles, H. Part III. Am. J. Dig. Dis., 17:119, 1950.
237. Necheles, H., Kroll, H., Bralow, S. P., and Spellberg, M. A. Part IV. Am. J. Dig. Dis., 18:1, 1951.
238. Hallabaugh, C. B., Burt, L. H., and Walth, A. P.: Ind. Eng. Chem., 37:943, 1945.
239. Brown, C. J., and Houghton, A. A.: J. Soc. Chem. Ind., 60:254, 1941.
240. Ivy, A. C., J. A. M. A., 132:1053, 1946.
241. Hay, J. L., Varco, R. L., and Code, C. F.: S. G. O. 75:170, 1942.
242. Necheles, H. and Meyer, J.: Am. J. Physiol., 110:686, 1935.
243. Sapoznik, H. I., Arens, R. A., Meyer, J. and Necheles, H., J. A. M. A., 104:1792, 1935.
244. Meyer, J., Scheman, L. and Necheles, H.: Arch. Int. Med. 56:88, 1935.
245. Necheles, H., Sapoznik, H. I., Arens, R. A., and Meyer, J.: A. J. Dig. Dis. and Nutr. 1:684, 1934.
246. Ott, E.: Cellulose and Cellulose Derivatives. Vol. 5. p. 784. Interscience Publ. Inc. 1943.
Werle, E.: Chem. Ztg. 63:320, 1941; Chem. Zent.bl. 1, 1280, 1941; Chem. Abstr. 37, 2807-8.
247. Scheinberg, S., Bralow, S. P., and Necheles, H.: Surgery 24:972, 1948.
248. Bralow, S. P., Spellberg, M. A., Kroll, H. and Necheles, H.: Evaluation of a new antacid in treatment of peptic ulcer. Exhibit A. M. A., Atlantic City, 1948.
249. Brick, I. B., A. J. Dig. Dis., 16:315-319, 1949.
250. Crohn, N., Olsen, Wm. H. and Necheles, H.: Surg. Gyne. & Obstr., 79:41-49, 1944.

MEDICAL APPLICATIONS OF ADSORPTION AND ION EXCHANGE MATERIALS

GUSTAV J. MARTIN, Philadelphia, Pa.

THE GASTROINTESTINAL TRACT is a manufacturing plant of such complexity as to dwarf any of modern man's industrial operations. Thousands of synthetic processes are constantly in motion; thousands of destructive metabolic mechanisms are functional. The bacteria forming as they do the basis of these ceaseless chemical reactions never rest. The products of intestinal bacterial metabolism may be beneficial to the host or they may be detrimental. As vitamins are synthesized in the gut, so are the toxic chemicals: histamine, tyramine, putrescine, cadaverine, skatole and indole. The body is exposed during every second of its existence to the metabolic products of bacterial life. Medical science has neglected this field and its importance is obvious.

Medically, the problem is one of restricting toxic chemicals to the gut and permitting the absorption of nutrients. It is even more; it is the problem of preventing through adsorption or some other mechanism the irritant action of chemicals of toxic nature in solution; it is the problem of preventing contact of irritant chemicals with the intestinal mucosa. Irritation to the intestinal mucosa will produce diarrhea; therefore any state manifesting diarrhea as a symptom should be a field for the study of adsorbing agents as therapeutic adjuvants.

PHYSICAL ASPECTS OF ADSORPTION

Adsorption is a physical phenomenon. In any heterogenous system there exists a state of surface energy which is reflected in surface tension. It has been demonstrated by physico-chemical means that those substances which decrease surface energy tend to concentrate at the interface, that is, at the point of contact of solid with liquid. This phenomenon of concentration at an interface is called adsorption. Adsorption does not bring into play the forces of primary valence; it is an equilibrium mechanism. This being so, the application of adsorption agents to medicine must not be considered as an absolute but rather as a relative mechanism. The Freundlich isotherm which is--

$$x/m \text{ equals } aC^b$$

expresses in detail the forces in operation. x represents the weight of the substance adsorbed in grams; m represents the weight of the adsorbent in grams; C represents the concentration of the solution at equilibrium; a and b are constants depending on the nature of the adsorbent and the substance which is adsorbed. The Freundlich isotherm is presented here to emphasize the a and b factors. These are the determinant of the selectivity of adsorbent or material to be adsorbed. These are the factors which must be given prime consideration in the study of the application of adsorbing agents to medicine. The obvious goal is to achieve the greatest adsorption per unit weight of adsorbent.

The exact nature of adsorption is not known. In some instances primary and secondary valences do play a role. This is clearcut in the so-called ion exchange mechanisms which will be discussed but there are equally clearcut systems in which an adsorption complex is forced—this in contradistinction to the salt formation of ion exchange.

The binding seen in adsorption is a surface phenomenon and the extent of the surface area determines the magnitude of the reaction that will take place. Measurements of surface area have been made but divergence of opinion exists. Thus, Garner, McKie and Knight (37) arrived at a figure of 66 square meters per gram of charcoal as the surface area, while Gustaver (45) obtained much higher values, concluding that one gram of charcoal possesses 600 square meters of surface area. Surface area is determined not only by particle size, an important factor but also by the nature and size of the capillary system which extends through many adsorption agents. The nature of the solvent is also a major factor in determining adsorption; however, in the system confronted by the medical research workers the solvent is always water. This factor will therefore not be discussed at this point. The

Submitted April 21, 1950.

Research Laboratories, The National Drug Company, Philadelphia, Pa.

hydrogen ion concentration, molarity (amount of dissolved solutes) and other factors do play a vital role in adsorption as studied by the medical scientist and must be considered. The marked variation in pH passing from gastric juice to intestinal juice is an example of the extreme variations to which a given adsorbent will be subjected. The degree to which adsorption can occur is illustrated by the manner in which alkaloids are taken up by aluminum silicate (Lloyd's reagent) (78). The affinity is so great and adsorption is so complete that no bitter taste can be detected either in the mother liquor nor on the adsorption complex, when such substances as quinine or strychnine are adsorbed.

The phenomenon of pseudo-adsorption plays a role in the medical applications of adsorptive agents. Pseudo-adsorption is defined as adsorption followed by a chemical change in the material which has been adsorbed, the chemical change being of such a nature as to inhibit the reversal of the adsorption process. Proteins of biological importance such as pepsin are frequently subject to this mechanism, the pepsin can be adsorbed but it is then denatured and the denaturation is irreversible. This makes it impossible to recover the adsorbed enzyme. Lindau and Rhodius (77) investigated the adsorption of gelatin and egg albumin on powdered quartz. The egg albumin was irreversibly absorbed on the quartz; it underwent actual coagulation. This phenomenon is of great importance in the field to be reviewed and should be emphasized.

The adsorption of water in biological processes is of paramount significance. This is the problem of gel formation and does not concern our present discussion excepting as an example well known to all. Quastel (104) emphasizes the importance of adsorption in enzymatic action. Quastel concludes: "Specificity of enzyme action is dependent upon three factors. 1. Specificity of adsorption. 2. The nature and strength of the polarizing field at the active center. 3. The constitution of the adsorbed molecule." There are many mechanisms in metabolism in which adsorption plays a vital role. Two examples are given. Beyond this, it is intended to restrict the discussion to medical applications of adsorptive chemical agents.

Considering the extreme importance of this sphere of medical therapeutics, it is disturbing that so little work has been done. The range of possible adsorbing agents is great: paper pulp, charcoals, anion exchange resins, cation exchange resins, synthetic sodium aluminum silicates; aluminum silicates including bentonite, kaolin, permutite; aluminum oxides such as Bauxite; oxides of silicon such as Fuller's earth, magnesium silicate, magnesium trisilicate, graphite, aluminum hydroxide; and others.

CHARCOAL

The therapeutic use of charcoal goes back to ancient times; it was used in the treatment of anthrax, epilepsy, vertigo, etc. One of its first applications was in the adsorption of poisons. Varonina (142) studied the relative adsorption capacities of granular carbons compared to finely powdered charcoals. The adsorption capacity was much lower in the granular forms. In a study designed to determine the most applicable type of charcoal, Laquer and Sluyters (69) compared the adsorptive capacity of various types for oxalic acid, potassium oxalate, mercuric chloride, strychnine nitrate, morphine sulfate, methylene blue and iodine. Supra Norite was reported as being markedly superior. Sjogren and Wallden (124) warn against any attempt to assume that the in vitro testing of adsorptive agents reflects their in vivo capacity to reduce the lethal dose of any given toxic agent. They had attempted to correlate the capacity of some 20 different medicinal charcoals to adsorb methylene blue with their capacity to protect the animal against mercuric chloride poisoning. The probability that charcoal will actually remove a toxic chemical from the gut wall was established by Dingemanse and Laquer (27) who found that 47% of the mercuric chloride was adsorbed from the gut wall by charcoal. The point of lack of correlation of in vitro adsorptive power with protective power in vivo was again emphasized by Joachimoylu (55) who determined the adsorptive power of charcoals for iodine and then checked their capacity to prevent poisoning by strychnine. There was no correlation whatever. Leibenson (71) makes the point clear that charcoal can even be used to decrease the toxicity of agents given subcutaneously. Thus, morphine is excreted through the gastrointestinal tract and can be effectively removed, preventing reabsorption.

Anderson (5) has recently determined the capacity of charcoal to adsorb strychnine, morphine, atropine sulfate, nicotine, mercuric chloride, diethylbarbituric acid and sulfanilamide. The studies were carried out both in vitro and in vivo. In 1946, he added (7) studies of medinal, alurate, dial, evipal, phanodorm, salicylic acid, phenol, alcohol and potassium cyanide. The importance of pH and concentration for maximum adsorption by a charcoal is emphasized by Anderson (6). He concludes that the maximum adsorption of nicotine which is a weak base occurs from dilute solutions at an alkaline pH. Weak acids such as phenols, barbiturates, etc., are best adsorbed at an acid pH. Ampholytes such as sulfanilamide are best adsorbed at the isoelectric point. Ethyl alcohol adsorption is unaffected by pH.

Whether or not adsorbing agents actually adsorb bacteria remains an open question. Gunnison and Marshall (44) found that the apparent adsorption of E. coli, Clostridium welchii and Lactobacillus acidophilus by particulate kaolin, Lloyd's reagent, calcium carbonate, aluminum hydroxide and barium sulfate in vitro was not marked. Charcoal did effectively remove Lactobacillus acidophilus but did not significantly remove E. coli and Clostridium welchii. Charcoal removed staphylococci. The general impression received from the work of these authors is that alterations in intestinal flora produced by administration of inert particulate agents are not due to adsorption of bacterial cells.

Charcoal definitely adsorbs toxins and anti-toxins, including diphtheria and tetanus. It is also able to adsorb viruses such as sheep pox and hoof and mouth disease. Kraus and Barbara (66) established the ability of charcoal to adsorb diphtheria, tetanus and dysentery toxins. Further studies (66a) demonstrated that rabbits which had received intravenous injections of dysentery toxin were saved by the administration of animal charcoal per os. Lemetayer and Uhry (72) attempted to reduce toxicity of tetanus toxin by intravenous injection of charcoal and reported that this was not possible. Charcoal failed to adsorb mussel toxin.

The constipating effect of charcoal was studied by Bauer (12) in rats. The administration of charcoal doubled the period required for material to pass through the intestinal canal. Charcoal likewise inhibited the increased peristalsis induced by castor oil.

CHARCOALS ADSORB HORMONES, VITAMINS AND ENZYMES

Extensive work has been done on the adsorption of enzymes and there is no need to review it beyond considering the action of these agents on the enzymes of the gastrointestinal

tract. Strauss (136) reported the adsorption of both hydrochloric acid and pepsin from gastric juice. Most recently, Alpert and Martin (4) reported that activated charcoal was highly effective in the inhibition of pepsin in vitro. 15 mgm. of charcoal per 5cc. completely inhibited the activity of 1.5 mgm. of 1:3000 NF pepsin per each 5 ml. In a similar study Moss and Martin (92) found that lysozyme was specifically inhibited by an activated carbon; however, the carbon was not as active as certain hydrated aluminum silicates.

The effectiveness of charcoals in adsorbing hormones is well illustrated by the work of Sklow (125) who tested animal and plant charcoals, kaolin, kieselguhr, Fuller's earth, calcium carbonate, benzoic acid, Lloyd's reagent and found that of these only the charcoals prolonged the action of estrogenic hormones following the implantation of adsorbates on the various agents. Somewhat similar efforts have been made to use charcoal adsorbates for the administration of various pharmacological agents. Goiffon (38) adsorbed eserine on charcoal and used it effectively in the treatment of atonia of the intestine. Through this technique they avoided secondary reactions. Similarly, these investigators used an adsorbate of hydroxyaminophenylarsonic acid against amebic, parasitic and certain bacterial infections of the gut. Lefeure (70) used atropine adsorbed on charcoal and strongly recommended it in the treatment of spasms of the intestine. Its action was more localized and general poisoning was impossible.

Koenig (60) listed the applications for charcoal in medicine as follows:

1. Acute poisoning with metal salts, such as mercuric chloride, arsenic, phosphorus, lead compounds; poisoning with organic compounds like strychnine, morphine, cocaine, nicotine and food poisoning.
2. Infectious diseases; cholera, dysentery, intestinal catarrh.
3. Autointoxication on the part of the intestine.
4. Hyperacidity of the stomach.
5. Ulcer ventriculi.
6. Intestinal complaints owing to excessive formation of gas and occurrence of large quantities of bacteria.

Charcoal is recommended today in therapeutics in severe diarrheal conditions, such as cholera, dysentery or ulcerative colitis. The dosage recommended is 1 to 5 grams, three or four times daily. Bastedo (10) states that in his experience charcoal has little or no value in above mentioned conditions.

The use of charcoal in poisoning is well established. In flatulency, charcoal is employed but its value is slight beyond the stomach. It is even questionable whether it has any value whatever in adsorbing gases once it has been moistened.

RECAPITULATION

Activated charcoal adsorbs toxins, hormones, vitamins and enzymes. It is extensively used in biochemical studies for these purposes. Clinically, the use of charcoal in poisoning with strychnine, etc., and its use in the treatment of diarrheas, is well established. It is not an effective agent in flatulence (20) nor is charcoal established as an effective therapy in the treatment of bacterial food poisoning (146). The degree of interference of charcoal with nutrition has not been established. There seem to be no prolonged feeding tests; the assumption is that charcoal is non-toxic and in a positive sense this is doubtless true; however, in a negative sense, there is an open question. Does charcoal remove vitamins, minerals when fed over a prolonged period? This point should be established.

ION EXCHANGE RESINS

The discovery by Adams and Holmes in 1935 (2) of ion exchange resins opened the field for the preparation of ion-free water by application of two-step ion exchange. These investigators found that polyhydric phenol-formaldehyde resins, when polymerized to the insoluble C stage, would exhibit the phenomenon known as base exchange. The reaction is governed by the law of mass action and is reversible in accord therewith. Adams and Holmes reasoned that an amine-formaldehyde resin would show removal of acids in consequence of basic groups present in the polymerized resin. In the case of these anion exchangers, the acid adsorbing action is accomplished by amino groups which form a part of the surface of large insoluble organic molecules. In other words, the anion adsorbent is pictured as a high molecular weight compound having throughout the lattice activated amino groups—(NH_2). These are capable of forming stable amino hydrochlorides and, thus, the acid is removed molecularly and fixed reversibly.

Matchett (83) has used acid adsorbing resins to isolate tartaric acid. Grape wastes are filtered through and the acid is adsorbed and subsequently removed with sodium carbonate. Formic acid is removed from formaldehyde in a similar manner (83) resulting in a better product of formaldehyde. Gaddis (36) has used Amberlite IR-4 in an unusual manner. He found that a stable compound was formed with hydrogen sulfide and that the resin would adsorb 12% of its weight of hydrogen sulfide. This additional compound was used in the analysis of Group II ions. Block (15) utilized resinous exchangers in the process of production of arginine, histidine and lysine. Meyers (83) reports that thiamine hydrochloride is adsorbed quantitatively on Amberlite IR-100.

Amberlite IR-4, or as it is now called Amberlite XE-43, is a polyethylene polyamino methylene substituted resin of diphenyloldimethylmethane and formaldehyde in basic form De-Acidite, which is also used as an antacid, is an aliphatic amine resin containing principally tertiary amine groups with some primary and secondary groups.

De-Acidite is called an anion exchanger, but the facts show that the free acid molecules react in much the same way that ammonia reacts with an acid (118).

Cleaver, Hardy and Cassidy (21) used both cation and anion exchange resin in the chromatographic adsorption of amino acids. The adsorption of any nutrient by a material to be considered in adsorption therapeutics is of great importance. If in vivo a similar adsorption were operative to a significant degree, the adsorbent would be eliminated from consideration for medicinal usage. In 1944, Steinberg (134) proposed the use of cation exchangers for the removal of calcium from blood samples which results in anticoagulant action.

Herr (51) applied the principle of ion exchange for the separation, recovery and concentration of thiamine. A somewhat similar application involved the purification of penicillin and other antibiotics using cationic and anionic exchangers (25).

The applications of polyamine formaldehyde anion exchange resins in therapeutics made their appearance in 1945 and 1946. Segal et al (119) and Martin and Wilkinson (81) established the non-toxicity of a polyaminoformaldehyde resin in chronic feeding tests followed by histopathological examination. At levels of 5 and 10%, even at 20%, there was no evidence of toxicity. The resin removed acid from gastric juice. Martin and Wilkinson noted an inactivation of pepsin as well as trypsin. In an acid pH (1.5) the resin adsorbed sodium chloride, sodium phosphate, ascorbic acid; however, at the pH of the intestinal tract (8.5) desorption was complete. The possible application of these anion exchange resins in a therapeutic management of peptic ulcers was suggested by both groups of investigators (81, 119). Extending their original observations Wilkinson and Martin (149) established the importance of particle size on speed of activity of the resin. Further work (82) established the fact that an anion exchange resin does not adsorb either thiamine or riboflavin but that it does adsorb strongly indole and skatole. Kaolin had no capacity to adsorb these products of intestinal putrefaction. Permutite (synthetic zeolite, sodium aluminum silicate) in the same study showed a powerful capacity to adsorb putrefactive amines such as tyramine, histamine and putrescine. Here, again, kaolin did not possess a capacity to adsorb amines. In this paper the suggestion was made that ion exchange material would be useful in confining to the intestinal tract certain putrefactive chemicals. A further conclusion was "Multiple adsorbing agents must be employed for effective action in the tract." The conclusions were based on in vivo as well as in vitro tests. The toxic effect of both indole and guanidine acetate was significantly lowered through the prophylactic application of exchange materials.

Clinical application of anion exchange resins came in 1947 with the publications of Spears and Pfeiffer (129) and of Kraemer and Lehman (65). Spears and Pfeiffer studied a series of 78 patients. Their conclusions were to the effect that there were no toxic reactions. In one series of 30 patients with peptic ulcer pain, all but one experienced pain relief. These investigators concluded that "An insoluble, non-absorbable anion exchange resin, having properties of speedy action and great acid neutralizing powers, which inhibits pepsin activity; which causes no acid rebound, no constipation and no removal of phosphate or chloride ions from the body fluids, and which has but a slightly unpleasant taste should be of value to patients with peptic ulcerations—." Kraemer and Pfeiffer studied a series of 18 cases and concluded: "They (anion exchange resin) are valuable substances for controlling gastric hyperacidity without the annoying side effects of constipation and diarrhea. They cannot upset the acid base balance of the blood." Since the first publication, Kraemer has extended his studies to cover some 150 patients (65, 65a) Weiss (154) studied 44 patients with x-ray proven gastric ulcers and obtained symptomatic relief in 40 with x-ray regression of the ulcer crater in 39 cases. Kasdon (59) made an interesting new observation on the therapeutic application of an anion exchange resin when he observed complete cure in 31 patients out of 35 with heartburn of pregnancy.

Implication of lysozyme in the etiology of ulcerative colitis came with the work of Meyer et al (100) who stated: "These data, together with experimental production by lysozyme of ulcerations in the canine alimentary tract, indicate that lysozyme is an etiologic agent which locally initiates the lesions of chronic ulcerative colitis." With this as the operative theory, Moss and Martin (92) studied a series of nearly 50 compounds to determine those most effective as inhibitors of lysozyme. Of the adsorptive agents, Fuller's earth, diatomaceous earth, kaolin, polyamine resin, and many sodium aluminum silicates proved ineffective. A synthetic zeolite, an activated carbon and a hydrate aluminum silicate (Bentonite) proved active. Various combinations of adsorbing agents were also tested. A synergism was shown by a combination of synthetic zeolite, polyamine resin and hydrated aluminum silicate (Bentonite).

Clinical results with a combination of a polyamine resin, a synthetic zeolite and a synthetic sodium aluminum silicate were reported in 1950. Joslin (58) first reported a series of 50 cases of infantile diarrhea and noted the combination of adsorbents as effective in 100%. Lichtman (75) found the use of polyphasic adsorption highly effective in food poisoning. Rafsy (108) applied the materials to a new field namely that of arthritis in the aged. Use of adsorptive agents as adjuncts to the application of chemotherapeutic chemicals was found beneficial by Quintos (106). Finally, Rollins (110) reported the efficacy of the combined adsorptive agents in ulcerative colitis.

The first report of the therapeutic application of cation exchange resins was that of Dock (28) who applied them in a therapeutic procedure for sodium depletion. He tested two resins both of which were sulfonic acid types. When these were fed to rats at a 10% level, no evidence of toxicity occurred in a two week experiment. Dock was able to increase fecal sodium from 3.3 to 5.1 mgm. per kilo of rat per day to a level of between 34 and 64 mgm. per day. The sodium uptake in the rat was 20 to 30 mgm. per gram of resin.

Greenblatt and Gilwood (40) reported the use of a cation exchanger in selected human subjects. They used the material to study urine excretion and edema. Calcium, potassium, magnesium were all removed simultaneously. They have not as yet reported the details of their investigations.

Another preliminary report by Gordon et al (39) indicated the non-toxic nature of calcium zeolite when administered in 30 gram doses daily. They suggest the use of calcium zeolite in congestive heart failure. Calcium zeolite is not a resin but its use for sodium removal indicated its mention with the cation exchange resins.

At the present time, it seems probable that cation exchange resins will find a place in the therapeutic management of cardiacs and hypertensives in those instances where low sodium intake is desired.

Kaolin

Kaolin is a native hydrated aluminum silicate. The application of this material in the field of medicine has received an extensive consideration. Kaolin is one of the oldest remedies used in medicine. The Greeks and the Persians used it. Chinese physicians have for centuries regarded it as a specific in the treatment of diarrheas. Meunier (89) used kaolin in a thick paste for hyperacidity and stomachic hypersecretion. Stumpf (137) and Stoerk (135) used large doses of kaolin around 30 to 45 grams in chronic dysentery. Excessive and prolonged administration of kaolin was questioned by Bungart (19) who noted accumulation of the adsorbent in the intestine. Serious complications were reported by this investigator to be exceptional. Strauss (136) and Petersen (103) reported the activity of digestive enzymes was inhibited by kaolin.

A novel application of kaolin was made by Hektoen and Rappaport (50) when they applied this material as a dry powder to the nose and throat in cases of diphtheria. They explained the mechanism as one of adsorption of bacteria. Later, Gunnison and Marshall (44) reported that kaolin had little capacity to adsorb bacteria such as E. coli, Clostridium welchii, and Lactobacillus acidophilus. Kaolin did remove Staph. aureas, Sarcina lutea and Bacillus subtilis. The alteration in intestinal flora produced by this agent could not therefore be attributed to the adsorption of bacteria. In 1915, Aaron (1) recommended kaolin in any state of inflamed or ulcerated intestinal mucous membrane. He also recommended its use in enteritis in doses of 60 to 100 grams. Consideration of the great effectiveness of kaolin in a colloidal state was made by White-Robertson (148) when he compared it with ordinary kaolin. This is the first consideration of the importance of particle size in the therapeutic application of adsorbents to be published.

The use of Kaolin in cholera was reported by Kulme (67) who stated that he reduced the mortality rate from 50% to 3%. Large doses of around 100 grams of kaolin were given each half hour. In 1921, Walker (143) provided the rationale for the use of kaolin. He concluded that its action was both mechanical and adsorptive. The mechanical action was stated to consist of the formation of an adherent coating on the wall of the gut and of enclosing and carrying with it a large number of bacteria. The use of kaolin was recommended in ulcerative colitis, cholera, diphtheria, ptomaine poisoning, bacillary diarrhea. Further establishment of the rationale for

kaolin came with the work of Eisler (31) who reported that kaolin combined with cholera vibriones but not with typhus bacilli.

A much more detailed report by Braafladt (17) demonstrated the neutralizing effect that kaolin had on toxins and toxic products of pathogenic intestinal microorganisms. His technique involved treating the cultures, centrifuging and then injecting the supernatant fluid into animals. Adsorption was offered as explanation of the successful use of kaolin in Asiatic cholera, bacillary dysentery acute enteritis, typhoid, meat poisoning, and in botulism. Kaolin combined with toxins and toxic products of Vib. cholerae, B. dysenteriae (Shiga), B. enteritidis, B. diphtheria, B. Botulinus, B. typhosus, B. paratyphosus B and seemed to combine with toxic products of putrefactive and proteolytic bacteria. Kaolin changed the bacterial flora of the gut from a predominantly proteolytic type to an aciduric one. Braafladt used kaolin in gastrointestinal disturbance in tuberculous patients with marked success. Extension of the use of kaolin to rheumatism, neuritis and asthma was made by Jordan (57) who also recommended its use in bronchitis, pharyngitis and infantile diarrhea. Measles, whooping cough and other children's diseases responded well to this therapeutic measure. Morning sickness of pregnancy was alleviated by kaolin. Bargen (9) used a mixture of kaolin, bismuth and tribasic calcium phosphate in the treatment of uncomplicated chronic ulcerative colitis. The mixture proved to be temporarily helpful.

Kaolin (3,4) did not inactivate pepsin in a ratio of 0.2 grams of kaolin to 0.3 grams of pepsin 1:3,000 NF. Kaolin (92) did not inactivate lysozyme in any concentration up to the maximum tested which was 10 mgm. per ml. in the presence of 10 to 200 units of lysozyme. The importance of the failure of kaolin in the inactivation of lysozyme becomes apparent in the light of the work of Myer et al., (100) who states: "These data, together with experimental production by lysozyme of ulcerations in the canine alimentary tract, indicate that lysozyme is an etiologic agent which locally initiates the lesions of chronic ulcerative colitis." A therapeutic regimen in the treatment of ulcerative colitis would necessarily have to inhibit the action of lysozyme if the above concept is correct.

In 1937, several reports (127) (32) appeared advocating combinations of kaolin and aluminum hydroxide. Smith (127) found the combination more effective in adsorbing bacteria from fecal samples. Eyerly and Breuhaus (32) obtained beneficial results in ulcerative colitis using retention enemas of kaolin and aluminum hydroxide. These investigators state that they believe the use of the combination to be rational because the adsorption of bacteria and their products reduces irritation and decreases the adsorption of toxins. The astringent action is also beneficial. The statement is made that no bolus or impaction formation occurred with moderate care. In that same year Fradkin (35) used a mixture of kaolin and aluminum hydroxide on patients with ulcerative colitis. The results were satisfactory except that the frequent administration of large doses of the mixture interfered with the patient's digestion and had to be discontinued. Fradkin then resorted to the use of a mixture of kaolin 20%, mineral oil 10% and gel of aluminum hydroxide 70% per rectum. The results of the treatment were strikingly beneficial. The therapy was recommended only in the convalescent patient whose stools continued to be streaked with blood. This same combination of kaolin and aluminum hydroxide was used by Swalm (138) in treating many gastrointestinal disorders. 85% of the patients were definitely improved by the medication. Swalm stressed the local action in the lumen of the stomach and intestine by virtue of its mildly astringent and adsorptive properties. He recommended its use in hypermotile states. The dosage was a tablespoonful of the mixture containing 20% kaolin and 2.5% aluminum hydroxide given three times daily. Shelanski et al (121) using three one ounce doses daily of a combined kaolin, aluminum hydroxide preparation, eliminated infection of Trichuris trichiura, oxyuris vermicularis, Ascaris lumbricoides, Strongyloides stercoralis, Hymenolepsis nana, Endamoeba coli, Endolimax nana, Iodamoeba butschlii, Dientamoeba fragilis, Retortamonas hominis, Chilomastix mesnil, Giardia lamblia and Trichomonas intestinalis. The treatment was continued for a period of three or four weeks. The only organism which persisted was Trichuris trichiura.

Spiesman (130) used combined aluminum hydroxide and kaolin and reported good results in chronic cases such as those of functional diarrhea, spastic colon and chronic ulcerative colitis. He recommended the use of the combination in the management of tropical dysenteries, diarrheas and functional colonic conditions.

Kaolin has been used in other combinations. For instance, Hayem (49) used a combination of bismuth subnitrate and kaolin in the treatment of gastrointestinal disturbances. A combination of kaolin and calcium gluconate was used by Greene and Block (41) in the treatment of bacillary dysentery. Kaolin alone and combined with calcium lactate or gluconate was found by Tumen (141) to be effective in diarrheas. He gave 1 dram (6.8 grams) four to eight times daily.

Stein and Kotin (133) found a combination of kaolin lactose and thiamine to be exceptionally beneficial in the treatment of avitaminosis and secondary anemia, together with diseased conditions of the gastrointestinal system.

The use of kaolin in food poisoning has been established by McRobert (86) and Schwartz (117). McRobert referred to an outbreak of bacterial food poisoning in Burma in 1932. Kaolin treatment was instituted and nothing more was required. Schwartz treated 110 patients suffering from acute gastroenteritis following a staphylococcal food poisoning. Kaolin and sedation were the only measures used and marked success was attained.

Attempts have been made to place the use of kaolin in food poisoning on a fundamental basis. Great differences had been found by Ben (107) between the adsorptive abilities of various kaolins. Muller (95) working with mussel poison reported that German kaolin would not remove more than 50% of the toxic substances from an aqueous solution. Activated charcoal was totally ineffective. Mutch (99) examined the use of kaolin in food poisoning in detail. Using a kaolin designated as No. 4 he found that per gram it adsorbed 94 mld of mussel toxin; 3.8 mgm. of muscarine, (the toxic agent of mushroom poisoning); 5 mgm. of solanine (toxic principle of green potatoes); 5 mgm. of histamine phosphate. This excellent data permits comparison with other adsorption agents under somewhat similar experimental conditions. For comparison purposes, 1 gram of an activated synthetic zeolite adsorbed approximately 30 mgm. of histamine (82).

The possible interference of kaolin with nutrition was indicated by the work of Nesserli (88) who demonstrated that rats and pigeons fed on a diet of decorticated rice developed an avitaminosis more rapidly and more severely if either charcoal or kaolin was added to the diet. The danger of any soluble aluminum preparations was pointed out by the work of Deobald and Elvehjem, (26) who found that rickets developed to a greater degree in chicks given oral doses of these compounds. They noted a definite drop in the blood phosphorus as early as the fifth day. Another possible complication of the use of kaolin is indicated by Long et al (79) who noted polyposis in the rat intestine produced by the incorporation of kaolin into the diet. They felt however that polyposis would be unlikely to occur in man when kaolin was used in the amounts ordinarily prescribed.

Melnick et al (87) demonstrated in human studies that while Fuller's earth did reduce markedly the availability of thiamine, kaolin did not interfere with thiamine utilization. These investigators make the point that the continuous use of large doses of adsorbing agents should not be assumed to be free of danger concerned with sufficient vitamin intake unless tests have been conducted.

RECAPITULATION

Kaolin through its adsorptive capacity has been established as being of value in mucous colitis, bacterial food poisoning, bacillary dysentery, amebiasis and other intestinal parasites, tuberculosis of the intestine and chronic ulcerative colitis. In general, it is not a specific and should be considered only as supportive treatment.

MAGNESIUM TRISILICATE

Magnesium trisilicate has been recommended for its adsorptive qualities. Mutch (98) stated the range of

its adsorptive affinities as covering acid and basic dyes, alkaloids, bacterial toxins, putrefactive amines and food poisons. One gram of the silicate removed 140 MLD of tetanus toxin. It had no affinity for the toxin of Amanita phalloides. The poison of mussel was adsorbed. In a second paper, Mutch (98a) stated that magnesium trisilicate was non-toxic and did not disturb the normal action of the bowel. He indicated the prolonged action of the compound in acid neutralization. Pepsin was adsorbed. One gram of the trisilicate neutralizes 310 cc. of N/20 hydrochloric acid (97) and its neutralizing action was reported to continue for several hours. The suggestion is made that hydrated silica is formed and that this material also possesses markedly beneficial adsorptive affinities. Many papers have appeared on the antacid qualities (97, 80, 96, 109, 68, 18, 111, 140, 101, 64, 123) and on the use of magnesium trisilicate in peptic ulcers (97, 53, 80, 96, 74, 63).

Page and Thomas (101) stated magnesium trisilicate to be an excellent antacid, antiseptic, antitoxic, and adsorbent material. They recommended one gram every one or two hours in the control of nonspecific food poisoning. This same dosage was effective in the control of acute nonspecific diarrheas. Page et al (102) studied excretion of silica by patients ingesting magnesium trisilicate. Excretion of silica was elevated but the author concluded the adsorbed silicate exerted no deleterious effect.

Schiffrin and Komarox (114) reported failure of magnesium trisilicate to inactivate pepsin at pH values of 1.0 to 2.0, therefore any effect it would have on peptic activity would be due to pH shift out of the optimal range of pepsin.

Criticism of the use of magnesium trisilicate first came from West and Pennoyer (147) who gave 6 grams daily and found serum calcium levels depressed with markedly increased magnesium levels. The magnesium blood levels were so high as to cause drowsiness. Interference with protein absorption was noted. On an average they report that 6.5% of the magnesium content of the trisilicate ingested was absorbed and excreted in the urine.

The irritative capacities of the magnesium ion have been recorded by Mutch and others (140, 123, 101, 96) who found that the dosage required for therapeutic response resulted in laxation.

Batterman and Ehrenfeld (11) reporting on the use of magnesium trisilicate in peptic ulcers stated that it was relatively ineffective for symptomatic relief and provided little improvement. 21% of the patients became worse 14% showed no change, and 64% showed some degree of improvement. When the dosage was raised (1 to 5 grams every four hours) to give adequate therapeutic effect gastrointestinal irritation occurred so that any observable beneficial effects were overshadowed by borborygmi, abdominal colic and laxation. They conclude that the use of magnesium trisilicate is not justified in the treatment of peptic ulcer.

ALUMINUM HYDROXIDE

Aluminum hydroxide has become the most generally used of all gastrointestinal adsorbents. It is not intended to review the literature on aluminum hydroxide in its entirety, rather to present an attempted analysis of those points permitting the medical research worker to analyze the situation to his own satisfaction. In 1929, Crohn (24) made the first report on the value of aluminum hydroxide in the treatment of peptic ulcer. The literature today is replete with papers (85, 56, 112, 111, 90, 128, 24, 22, 150) covering the therapeutic value of aluminum hydroxide preparations. It was the first non-systemic antacid (30) and there are few today who debate the dangers of alkalinizing the body with soluble antacids (115, 111). A second point favoring aluminum hydroxide is its reported capacity to inactivate pepsin. The importance of pepsin in the production of peptic ulcers has been repeatedly demonstrated. The entire emphasis of the concept of etiological factors in gastric and duodenal ulcers has shifted from hydrochloric acid to a recognition of the dominant role of pepsin.

Schiffrin and Warren (115) using cats, perfused isolated loops of small intestine with hydrochloric acid and pepsin and produced typical ulcers. Hydrochloric acid alone was not as productive of ulcers. The duodenum, in the absence of biliary and pancreatic secretion, was more susceptible to the action of acid alone than was either the jejunum or ileum. Driver et al (29) and Matzner et al (84) obtained similar results in rats and dogs. Recently, LeVeen (73) reported the production of ulcers in the small bowel of dogs through irrigation with acid pepsin solutions. Evidence was presented showing that this effect of acid is dependent upon its enhancement of pepsin action rather than injury by acid. Commenting editorially in the same issue of Gastroenterology (43) Grossman states "There is little question that pepsin enormously increases the injurious effect of acid." It is generally felt that a highly effective therapeutic agent in peptic ulcer must not only alter acid concentrations but must primarily reduce pepsin activity. Complete elimination of peptic activity would not be fatal to protein digestion because the intestinal enzymes are quite capable of digesting protein (16).

A given agent may eliminate the action of pepsin and thus bring about a therapeutic effect either directly or indirectly. Indirectly, the action is via altered pH with reduced peptic activity due to that alteration. Directly, it may prevent the action of the enzyme without changing the pH. If the agent reduces peptic activity there will be a therapeutic effect even if no change in hydrogen ion concentration is produced. It is probable that excessive reduction of gastric acidity is illogical (90) as the antibacterial action of the highly acid gastric content would be eliminated, thus permitting living bacteria to pass through to the intestine. This is a decidedly unphysiological state. Spallanzani and Beaumont observed the antiseptic action of gastric juice. It is well-known that persons having a copious and active gastric juice are less liable to infection by typhoid and cholera than those with less acid juice. The acid gastric juice provides protection against parasites of all kinds, bacteria, moulds, protozoa, etc. The acidity is particularly important in the checking of fermentation. Any reduction in gastric acid is apt to be followed by a bacterial or yeast fermentation in the stomach which may produce irritating organic acid and gas.

With the foregoing facts in mind, the importance of reports that aluminum compounds precipitate pepsin at low pH are of obvious importance (62, 115, 111, 61, 113, 114). The basis of this precipitating of pepsin is through the reaction of aluminum ions with the protein molecule forming an aluminum proteinate. It is extremely probable that this same formation of aluminum ions responsible for reaction with pepsin is the factor causing constipation and even the production of intestinal obstruction by the continued use of aluminum preparations (48). Kraemer (63) had previously reported frequent constipation and the occurrence of fecal impaction in two cases. The case reported by Havens was one with a bleeding duodenal ulcer. Aluminum hydroxide was used for its astringent effect which must be based on the presence of aluminum ions and the reaction of those aluminum ions with proteins. He felt that there was danger in the use of aluminum preparations in older or very ill patients whose energy is depleted and whose intestinal tract may lack normal tonus.

Schiffrin and Komarov (115) found aluminum phosphate to be markedly inferior to aluminum hydroxide in relative capacity for pepsin inactivation. Aluminum phosphate is also less constipating than is the hydroxide (150). It has been suggested that direct correlation of pH changes and peptic activity reduction exists (122) but the majority of evidence strongly indicates pepsin precipitation by aluminum ions. Certainly, aluminum hydroxide produces no change in gastric emptying time and has no effect on motility of either the stomach or the pyloric antrum (105).

Many other possibilities for favorable therapeutic actions by aluminum hydroxide are apparent. The colloid would

probably adsorb toxin generally because it is known to adsorb diphtheria antitoxin (47) and diphtheria toxins (116). The use of aluminum hydroxide as one component of an intestinal adsorbent preparation was proposed by Wallbach (144) who found that no single adsorbent was effective against all diarrhea producing agents; thus, aluminum silicate was most active against podophyllin, bolus alba against castor oil, etc. He used a mixture of equal parts of animal charcoal talcum and aluminum hydroxide in his adsorptive combination. Kaolin alone is not as effective as kaolin plus aluminum hydroxide for the removal of fecal matter (127).

It is necessary that constant vigilance be maintained for differential adsorption, i.e., the differences between the capacity of any given adsorption agent to remove harmful elements and to remove dietary ingredients vital to life. Beazell, Schmidt, and Ivy (13) first undertook an investigation of this type. In dogs, they reported that aluminum hydroxide did not alter the nitrogen nor the fat content of the feces. This was interpreted to indicate no major interference with digestion. Similar findings were reported by Grondahl and and West (42) who found in human subjects no interference by aluminum hydroxide with carbohydrate, fat or protein utilization. Interference with both vitamin A nutrition and phosphate metabolism by aluminum gels was reported in 1946 by Hoffman and Dyniewicz (52). Aluminum phosphate gels did not interfere with vitamin A tolerance curves, indicating no interference with this phase of nutrition. Some disturbance of amino acid, ascorbic acid and glucose metabolism was reported; by contrast, fat metabolism seemed normal. Aluminum hydroxide was reported to reduce the available phosphate to such a degree that it might interfere slightly with phosphorylation. Fauley et al in 1939 and 1941 (33, 34) had reported the unfavorable effect of aluminum hydroxide on phosphate adsorption in the absence of pancreatic secretion. These same investigators found aluminum phosphate completely satisfactory in this respect.

The aluminum ions bring about the precipitation of pepsin, the astringent effect and the constipation; it was therefore interesting to see what a so-called non-reactive aluminum hydroxide gel would do clinically. Smith (126) failed to find any difference from the standpoint of therapeutic efficacy between reactive and non-reactive gels. She reported the advantage of the non-reactive gel as "lack of any taste and the decreased incidence of nausea and constipation in patients receiving this medication." Non-reactive aluminum hydroxides are produced by precipitation of the hydroxide gel from aluminum chloride and a great excess of ammonium hydroxide. The aluminum hydroxide thus formed is in a non-reactive state and will not dissolve in 0.1 N. hydrochloric acid. It is an open question whether or not this material can be produced commercially. The probabilities are strong that it is only a laboratory curiosity. The fact remains that the less reactive the aluminum hydroxide, the less aluminum chloride is formed and the constipation will as a result be minimized. A product which is currently marketed containing an essentially non-reactive gel of aluminum hydroxide and magnesium trisilicate has received favorable clinical recognition (120, 22, 96).

Aluminum phosphate possesses less pepsin inactivating capacity, is less apt to produce phosphate loss, and is not as constipating as aluminum hydroxide; all of which is due to a decreased formation of aluminum ions. Again, many favorable clinical reports are available. Lichstein, Simkins and Bernstein (76) report favorable therapeutic activity with lowered incidence of constipation and no changes in mineral metabolism. Fauley and his associates (33) emphasize the interference by aluminum hydroxide of phosphate absorption and point out that aluminum phosphate does not share this fault. They state that the phosphate is definitely superior to aluminum hydroxide in patients with a relative or an absolute deficiency of pancreatic juice, or diarrhea or a low phosphorous diet. Emphasis on adequate dosage is the key to the work of Upham and Chaikin (141a). They found dosages of three tablespoonfuls every two hours and six tablespoonfuls at night to be essential for therapeutic efficiency. These investigators noted constipation in their patients.

Thus, it seems that the major problem of the clinical application of the aluminum preparations is constipation. Batterman and Ehrenfeld (11) report from 16 to 33% incidence of constipation in patients treated with reactive aluminum hydroxide gels; 30 to 35% with non-reactive aluminum hydroxide gels; 22% with aluminum phosphate; 14-15% with magnesium trisilicate; 20% with sodium aluminum silicate; 29.2% with a mixture of calcium caseinate and calcium carbonate; 9.7% with a mixture of magnesium trisilicate, oxide and calcium carbonate. Of the antacid preparations tried, a combination of non-reactive aluminum hydroxide and magnesium trisilicate gave the best ratio of effectiveness to incidence of constipation.

BISMUTH

Bismuth subgallate and bismuth subsalicylate were once in general use as intestinal protectives and mild antiseptics. These salts have been largely replaced by bismuth subnitrate and bismuth subcarbonate which when administered orally give mechanical protection to inflamed and irritated mucous membranes of the gastrointestinal tract. The bismuth goes into solution to some degree and the result is astringence. In the colon the bismuth salts are converted into the black sulfide from and also by reduction to metallic bismuth. Cases of nitrite poisoning have been reported from the use of bismuth subnitrate.

Bismuth salts were introduced into medicine in 1785 by Odier of Geneva. The use of bismuth subnitrate in the treatment of amoebic dysentery has been largely supplanted by modern procedures. Actually, the bismuth salts have very low amebicidal powers. The value of bismuth in amebic dysentery was due to its effect in controlling the diarrhea. Beck in 1909 (14) first reported evidence on the toxicity of bismuth salts. The subnitrate was found to be reduced by certain bacteria in the intestines of children with resultant nitrite formation and the production of methemoglobinemia. Deaths were observed. Children and patients with intestinal putrefaction were reported to be the most susceptible to nitrite poisoning resulting from the administration of bismuth subnitrate. Confirmation of these findings is ample (54) (23). Stieglitz (131) proposed the use of bismuth subnitrate for the prolonged continuous liberation of nitrites which would prove of value in the treatment of hypertension. Extending his original observations, Steiglitz (132) reported the reduction of subnitrate by E. coli. The nitrite produced varied in accordance with the number of bacteria, the pH, the amount of nitrate available, etc. The blood concentration of nitrite was increased three to four fold with a corresponding decrease in the arterial tension. Ayman (8) failed to note any favorable effect of bismuth subnitrate in well controlled cases of hypertension. This application has not found a place in the medical armamentarium.

The use of bismuth salts in the treatment of ulcerative colitis has been in recent times largely replaced by the use of other adsorptive materials. It seems that in general bismuth in large doses becomes detrimental by covering the intestinal mucosa with concretions. Methemoglobinemia has been reported to occur in patients with ulcerative colitis undergoing treatment with bismuth subnitrate (91).

The bismuth salts seem to possess no merit when compared to other inactive, inert adsorbing agents with the same or greater adsorptive capacity.

BARIUM SULFATE

Barium sulfate is extensively used in roentgenology but has never found application as an intestinal adsorbent. It is probable that fear of barium poisoning limits its general application; although dosages of 300-400 grams are commonly given in suspension form prior to x-ray.

BENTONITE

Bentonite is a colloidal, hydrated aluminum silicate. When added to water the dry powder swells to approximately twelve times its volume and forms a gel. It has great adsorptive capacity. Bentonite is an excellent suspending agent and is widely used in pharmaceutical preparations. It is used with nicotine as an anthelmintic in veterinary medicine (47a).

Bentonite should receive increasing attention in the future as an adsorbent as it has been demonstrated to inhibit lysozyme (92), pepsin (4), and trypsin (3), to remove toxic substances from bacterial lysates (94), to adsorb paralytic shellfish poison (139), and to adsorb effectively toxic chemicals of endogenous origin such as hystamine, tyramine, indole, etc. (3a).

CONCLUSIONS

It is certain that many toxic chemicals are produced in the gut as a result of bacterial metabolism. It is probable that long continued exposure to these toxic metabolites will result in damage to the body economy. From these premises, the logic of controlling the production and adsorption of these toxic agents becomes apparent. Medical science has in some degree approached the problem from the therapeutic standpoint; from the prophylatic standpoint, nothing has been done. With the growing importance of geriatrics and of the degenerative diseases, medical science can no longer afford to ignore the metabolic and anabolic madhouse which is the gastrointestinal tract when degenerative diseases come under consideration. It is the author's view that one factor in the degenerative diseases of aging is the long continued exposure of the body to toxic metabontes which are absorbed in small amounts from the gastrointestinal tract.

Of the large number of adsorption agents currently available, relatively few have been studied from even a few angles and virtually none has been studied in relationship to even the major enzymatic mechanisms active in the tract. Results in this field will be difficult of attainment and demonstration but the goal would seem to warrant the attempt. The medical application of adsorption and ion exchange materials is in its infancy but it will become the medical giant of tomorrow.

BIBLIOGRAPHY

1. Aaron, C. D.: Dis. of the Dig. Organs, Lea and Febiger, Phila.
2. Adams, B. A., and Holmes, E. L.: J. Soc. Chem. Ind. 54, 1-6T, 1935.
3. Alpert, S. and Martin, G. J.: Unpublished data. Rev. Gastroent., in press.
3a. Alpert, S. and Martin, G. J.: Am. J. Dig. Dis., in press.
4. Alpert, S. and Martin, G. J.: Am. J. Dig. Dis., 16, 10, 1949.
5. Anderson, A. H.: Dansk. Tids. Farm., 18, 21, 1944.
6. Anderson, A. H.: Acta pharmacol. toxicol., 3, 199, 1947.
7. Anderson, A. H.: Acta pharmacol. et toxicol., 2, 69, 1946.
8. Ayman, D.: JAMA, 98, 545, 1932.
9. Bargen, J. A.: Northwest Med., 30, 205, 1931.
10. Bastedo, Walter Arthur: Pharmacology, Therapeutics and Prescription Writing, Saunders, 1947, Phila.
11. Batterman, R. C. and Ehrenfeld, I.: Gastroenterology, 9, 141, 1947.
12. Bauer, H.: Arch. exptl. Path. Pharm., 134, 185, 1928.
13. Beazell, J. M., Schmidt, C. R. and Ivy, A. C.: Am. J. Dig. Dis., 5, 164, 1938.
14. E. G. Beck: J. A. M. A., 52, 14, 1909.
15. Block, R. J.: Proc. Soc. Exptl. Biol. Med., 51, 252, 1942.
16. Bockus, H. L.: Gastroenterology, Vol. 2, Phila. and London, W. B. Saunders Co., 1944.
17. Braafladt, L. H.: J. Inf. Dis., 33, 434, 1923.
18. Breuhaus, H. C. and Eyerly, J. B.: Ann. Int. Med., 14, 2285, 1941.
19. Bungart, 1917. (Reference in Sollman, T., A Manuel of Pharmacology, W. B. Saunders, 1942).
20. Calvert, R. L.: J. Am. Pharm. Assoc., 11, 798, 1922.
21. Cleaver, C. S., Hardy, R. A. and Cassidy, H. G.: J. Am. Chem. Soc., 67, 1343, 1945.
22. Collins, E. N.: J. A. M. A., 127, 899, 1945.
23. Constantinescu, C. D. and Jonescu, A.: Presse Medicale, 28, 155, 1920.
24. Crohn, B. B.: J. Lab. Clin. Med., 14, 610, 1929.
25. Cruz-Coke, E., Gonzales, F., and Hulsen, W.: Science, 101, 340, 1945.
26. Deobald, H. J., and Elvehjem, C. A.: Am. J. Physiol., 111, 118, 1935.
27. Dingemanse, E. and Laqueur, E.: Biochem. Z., 169, 233, 1926.
28. Dock, W.: Tr. A. Am. Physicians, 59, 282, 1946.
29. Driver, R. L., Chappel, R. H. and Carmichael, E. B.: Am. J. Dig. Dis., 12, 166, 1945.
30. Einsel, I. H. and Rowland, V. C.: Ohio State Med. J., 28, 173, 1932.
31. Eisler, M.: Biochem. Z., 150, 350, 1924.
32. Eyerly, J. B. and Breuhaus, H. C.: J. A. M. A., 109, 191, 1937.
33. Fauley, G. B., Freeman, S., Ivy, A. C., Atkinson, A. J., and Wigodsky, H. S.: Arch. Int. Med., 67, 563, 1941.
34. Fauley, G. B., Ivy, A. C., Terry, L., and W. B. Bradley: Am. J. Dig. Dis., 5, 792, 1939.
35. Fradkin, W. Z.: J. Lab. Clin. Med., 22, 896, 1937.
36. Gaddis, S. J.: J. Chem. Education, 19, 327, 1942.
37. Garner, W. E., McKie, D., and Knight, B.: J. Phys. Chem., 31, 641, 1927.
38. Goiffon, R.: Semana med., 37, 1133, 1930.
39. Gordon, G. B., Weitzner, H. A. and Barnard, R. D.: Ohio J. Sci., 48, 65, 1948.
40. Greenblatt, I. J., and Gilwood, M. E.: Proc. A. C. S. Meetings, Chicago, April 19 to 23, 1948.
41. Greene, B. L. and Block, L. H.: Am. J. Dig. Dis., 5, 684, 1938.
42. Grondahl, R. D., and West, E. S.: Am. J. Dig. Dis., 12, 197, 1945.
43. Grossman, M. J.: Gastroenterology, 8, 679, 1947.
44. Gunnison, J. B., and Marshall, M. S.: J. Bact., 33, 401, 1937.
45. Gustaver, B.: Kolloidchem. Beihefte, 15, 185, 1922.
46. Hanszen, A. H., and Selle, W. A.: Proc. Soc. Exp. Biol. Med., 54, 225, 1943.
47. Hansen, A.: Compt. Rend. soc. biol., 129, 216, 1938.
47a. Harwood, P. D. and Sturz, D. L.: Proc. Helminthal. Soc. Washington, 12, 1, 1945.
48. Havens, W. P.: J. A. M. A., 113, 1564, 1939.
49. Hayem, G.: Bull. acad. med., 106, 224, 1931.
50. Hektoen, L., and Rappaport, B.: J. A. M. A., 64, 1985, 1915.
51. Herr, D. S.: Industrial and Engineering Chem., 37, 631, 1945.
52. Hoffman, W. S., and Dyniewicz, H. A.: J. Lab. and Clin. Med., 31, 497, 1946.
53. Hurst, A. F.: The Practitioner, 137, 409, 1936.
54. Ionescu, A.: Bull. Soc. Chim. Romania, 1, 80, 1919.
55. Joachimoglu, G.: Chem. Z., 44, 780, 1920.
56. Jones, C. R., Jr.: Penna. M. J., 43, 468, 1940.
57. Jordan, A. C.: Lancet, 1, 432, 1923.
58. Joslin, C. Loring: Delaware State Med. J., in press.
59. Kasdon, S. C.: New Eng. J. Med., 239, 575, 1948.
60. Koenig, Franz: Pharm. Ztg., 73, 1602, 1928.
61. Komarov, S. A., and Komarov, O.: Am. J. Dig. Dis., 7, 166, 1940.
62. Komarov, S. A.: Rev. Gastroenterol., 9, 165, 1942.
63. Kraemer, M.: Am. J. Dig. Dis., 5, 422, 1938.
64. Kraemer, M.: Am. J. Dig. Dis., 8, 56, 1941.
65. Kraemer, M., and Lehman, D.: Gastroenterology, 8, 202, 1947.
65a. Kraemer, M.: Conn. State Med. J., 12, 305, 1948.
66. Kraus, R., and Barbara, B.: Deut. Med. Wschr., 41, 393, 1915.
66a. Kraus, R., and Barbara, B.: Wiener Klin. Wschr., 28, 524, 1915.
67. Kuhne, V.: Revue Med. Suisse Romande, 38, 555, 1918.
68. Kurtz, P.: J. Lab. and Clin. Med., 24, 1015, 1939.
69. Laquer, E., and Sluyters, A.: Biochem. Z., 156, 303, 1925.
70. Lefevre: Semana med., 1930, II, 133.
71. Leibenson, E. A.: Zhurnal. exptl. Biol. Med., 10, 58, 1928.
72. Lemetayer, E., and Chry, P.: Compt. rend. soc. biol., 125, 823, 1937.
73. LeVeen, H. H.: Gastroenterology, 8, 648, 1947.
74. Levin, M. B.: Am. J. Dig. Dis., 4, 574, 1937.
75. Lichtman, A. Lee: J. A. M. A., in press.
76. Lichstein, J., Simkins, S., and Bernstein, M.: Am. J. Dig. Dis., 12, 65, 1945.
77. Lindau, G., and Rhodius, R.: Z. physik. Chem., A-172, 321, 1935.
78. Lloyd, J. U.: Lloyd's Reagent, J. Am. Pharm. Assoc., 5, 381, 1916.
79. Long, C. F., et al: J. Lab. Clin. Med., 20, 475, 1935.
80. Mann, W. N.: Guy's Hosp. Rep., 87, 151, 1937.
81. Martin, G. J., and Wilkinson, John: Gastroenterology, 6, 315, 1946.
82. Martin, G. J., and Wilkinson, J.: Arch Biochem., 12, 95, 1947.
83. Matchett, J. R., and Meyers, F. J.: Ind. Eng. Chem., 35, 858, 1943.
84. Matzner, J. J., Windwer, C., Sobel, A. E., and Polayes, S. H.: Proc. Soc. Exp. Biol. Med., 34, 243, 1936.
85. McIntosh, J. F., and Sutherland, C. G.: Canad. M. A. J., 42, 140, 1940.
86. McRobert, G. R.: Brit. Med. J., 2, 304, 1934.
87. Melnick, D., et al: J. Nutrition, 30, 233, 1945.
88. Messerli, N.: Arch. Internal. de Physiol., 19, 103, 1922.
89. Meunier, L.: Bull. des Sci. Pharmacologiques 20, 641, 1913.
90. Miller, T. G.: Med. Clin. N. Amer., 28, 403, 1944.
91. Miller, R. C.: Proc. Staff Meetings Mayo Clinic, 19, 308, 1944.
92. Moss, J. N., and Martin, G. J.: Am. J. Dig. Dis., 15, 412, 1948.
93. Moss, J. N., and Martin, G. J.: Unpublished data.
94. Moss, J. N., and Martin, G. J.: Am. J. Dig. Dis., 17, 18, 1950.
95. Mueller, H.: J. Pharm. and Exp. Therap., 53, 67, 1935.
96. Mutch, N.: Brit. Med. J., 2, 735, 1937.
97. Mutch, N.: Brit. Med. J., 1, 254, 1936.
98. Mutch, N.: Brit. Med. J., 1, 143, 1936.
98a. Mutch, N.: Brit. Med. J., 1, 205, 1936.
99. Mutch, N.: Brit. Med. J., 1, 595, 1937.
100. Meyer, K., Prudden, J. F., Lehman, W. L., Gellhorn, A., and Steinberg, A.: Am. J. Med., 5, 496, 1948.
101. Page, R. C., and Thomas, E. G.: Mil. Surg., 85, 307, 1939.
102. Page, R. C., Heffner, R., and Frey, A.: Am. J. Dig. Dis., 8, 13, 1941.
103. Petersen, S. R.: Mikrochemie, 12, 215, 1932.
104. Quastel, J. H.: Trans. Faraday Soc., 26, 853, 1930.
105. Quigley, J. P., Einsel, I. H., and I. Meschan: J. Lab. Clin. Med., 24, 485, 1939.
106. Quintos, F. N.: Philippine Medical J., in press.
107. Rae, J.: Pharm. J., 121, 150, 1928.
108. Rafsky, Henry A.: Personal Communication.
109. Reid, C. G.: Am. J. Digest. Dis., 6, 267, 1939.
110. Rollins, C. T.: Personal Communication.

111. Rossett, N. E., and Flexner, J.: Ann. Int. Med., 18, 193, 1943.
112. Rutherford, R. B. and Emery, E. S., Jr.: N. E. J. Med., 220, 407, 1939.
113. Schiffrin, M. J., and Komarov, S. A.: (Unpublished data).
114. Schiffrin, M. J., and Komarov, S. A.: Am. J. Dig. Dis., 8, 215, 1941.
115. Schiffrin, M. J., and Warren, A.: Am. J. Dig. Dis., 9, 205, 1942.
116. Schmidt, S.: Biochem. Z., 278, 257, 1935.
117. Schwartz, I. R.: Gastroenterology, 6, 105, 1946.
118. Schwartz, M. C., Edwards, W. R., and Boudreaux, G.: Ind. Eng. Chem., 32, 1462, 1940.
119. Segal, H. L., et al: Gastroenterology, 4, 484, 1945.
120. Seley, S. A.: Am. J. Dig. Dis., 13, 238, 1946.
121. Shelanski, H. A., et al: J. Parasitol., 28, Suppl., 10, 1942.
122. Shoch, D., and Fogelson, S. J.: Proc. Soc. Exp. Biol. and Med., 50, 304, 1942.
123. Silverman, D. N., and Katz, R. A.: South. Med. J., 34, 638, 1941.
124. Sjogren, B., and Wallden, E.: Svensk. Farm. Tid., 39, 617, 632, 673, 697, 720, 1935.
125. Sklow, J.: Endocrinology, 32, 109, 1943.
126. Smith, Frances H.: Gastroenterology, 8, 494, 1947.
127. Smith, W.: Lancet, 1, 438, 1937.
128. Spangenberg, J. J., Muniz, L., and Garcia, Lemos M.: Dia Med., 13, 898, 1941.
129. Spears, M., and Pfeiffer, M.: Gastroenterology, 8, 191, 1947.
130. Spiesman, M. G.: Rev. Gastroenterol., 10, 191, 1943.
131. Stieglitz, E. J.: J. A. M. A., 95, 842, 1930.
132. Steiglitz, E. J., and Palmer, A. E.: J. Pharmacol., 56, 216, 1936.
133. Stein, D., and Kotin, E. H.: Clin. Med. Surg., 44, 115, 1937.
134. Steinberg, A.: Proc. Soc. Exp. Biol. and Med., 56, 124, 1944.
135. Stoerk, 1915 (Reference in Sollman, T.: A Manuel of Pharmacology, W. B. Saunders, 1942.)
136. Strauss, H.: Deut. Med. Wschr., 42, 36, 1916.
137. Stumpf, I.: Munch. Med. Woch., 61, 2030, 1914.
138. Swalm, W. A.: Med. Record., 140, 26, 1934.
139. Swayne, V. R., Jr., and Martin, G. J.: Am. J. Dig. Dis., (in press).
140. Tidmarsh, C. J., and Baxter, R. G.: Canad. M. A. J., 39, 358, 1938.
141. Tumen, H. J.: Northwest Med., 41, 42, 1942.
141a. Upham, R., and Chaikin N. W.: Rev. of Gastroenterology, 10, 287, 1943.
142. Bryzhin, F. F.: Farmakol. i, Toksikol., 8, 43, 1945.
143. Walker, R. R.: Lancet 2, 273, 1921.
144. Wallbach, G.: Arch. intern. de pharmacodynamie, 50, 143, 1935.
145. Weiss, J.: Review of Gastroenterology, 15, 826, 1948.
146. Werch, S. C.: Bull. U. S. Army Med. Dept., 8, 199, 1948.
147. West, E. S., and Pennoyer, C.: Am. J. Dig. Dis., 12, 199, 1945.
148. White-Robertson, A.: Pharm. J., 109, 396, 1922.
149. Wilkinson, J. and Martin, G. J.: Arch. Biochemistry, 10, 205, 1946.
150. Winkelstein, A., Cornell, A., Hollander, F.: J. A. M. A., 120, 743, 1942.

THE BEHAVIOR OF CAROB GUM IN THE GASTROINTESTINAL TRACT OF MAN

ARTHUR ANDREWS HOLBROOK, M. D., Milwaukee, Wis.

CONSTIPATION IS PROBABLY the most common symptom suffered by mankind. To be impressed by the implication of this statement one need merely consider the multitude of means man has employed to obtain relief from constipation: enema, colonic irrigation and suppository; salines, aloes, cascara, senna, licorice and rhubarb; calomel, phenolphthalein and sulfur; oils (mineral and castor), gums and so forth. The tragedy of constipation is that due to the ready availability of all these means, the sufferer for a time finds no difficulty in treating himself, little realizing that his symptom may be the first indication of some organic disease like bowel malignancy. The physician should prescribe for every patient with constipation. It is the purpose of this communication to present a new preparation which promises to be highly useful in this respect.

The preparation under discussion is called "Vacuosa."* Its active principle, the hemicellulose of the carob seed, is literally as old as the hills, being derived from the bean (fruit) of the Locust Tree, known in biblical times as St. John's Bread Tree. This leguminous plant is native to the shores of the Mediterranean. The gum from the carob bean has marked hydrophilic potency and thus fits into the same category as the vegetable gums of agar, acacia, tragacanth, karaya and psyllium seed, all of which are transformed to a colloidal state. There are, however, conspicuous differences in the rate of such transformation, the consistency (viscosity) of the colloid produced and the volume of the gel mass.

Comparative studies of the physical properties of the gums in common use have been published by Badosa, Serrallach and Monroset (1). They found by in vitro experiments that carob gum placed in water swelled into a colloid mass much more efficiently when shaken for an hour than when left standing. The degree of swelling was not appreciably influenced by changes in pH nor by gastric or duodenal juices. The viscosity of the gel formed by carob gum was about 9 times greater than that produced by other gums. Finally, the hemicellulose of the locust bean was apparently not subject to the digestive process, since incubation with digestive juice at 37°C. showed that no reducible sugars could be detected.

These studies have been extended in the laboratory of the author. It was observed that 10 cc. of carob gum granules, stirred every 5 minutes in a graduate containing 500 cc. of water at 37°C. (thus crudely imitating peristaltic agitation in the gastrointestinal tract), in 4 hours will progressively swell to reach a maximum bulk of 77 cc. Approximately the same rate of increase in volume occurs in a 0.2 N NaOH solution; however, in a 0.2 N HCl solution the final volume of gel after 4 hours is 55 cc. At the end of 1 hour there is no apparent difference in volume due to the pH of the media.

METHODS AND RESULTS

The principal purpose of this investigation was to determine the behavior of carob gum ("Vacuosa") in the gastrointestinal tracts of human beings.

Initially, attempts were made by using roentgenological techniques to identify any space-occupying mass within the colon after ingestion of "Vacuosa" Pelloids, employing barium suspensions as a contrast medium. The barium suspension, consisting of 2½ heaping teaspoonfuls of the powder in 8 oz. of water, was given at 10 P.M., and a flat plate of the abdomen was taken at 10 A.M. the following morning. This film served as a control. The procedure was repeated 2 days later in the same fashion except that, in addition, the subject took 2 heaping teaspoonfuls of "Vacuosa" with water immediately following the barium. This type of experiment was performed 12 times on 8 individuals with slight variations in technique. The differences produced by "Vacuosa" in the size of the lumen and character of the haustra of the large bowel were not conclusive with this technique.

The second phase of x-ray studies was devised so as to follow "Vacuosa" in its passage through the entire gastrointestinal tract. In view of the results in the

Submitted April 14, 1950.

*Supplied by Ayerst, McKenna & Harrison, Ltd., New York, New York.

initial experiences it was considered desirable to have the radiopaque material more intimately incorporated with the carob gum. Therefore, Pelloids containing equal parts of "Vacuosa" and barium were prepared. Two level teaspoonfuls of this experimental preparation weighed 8 grams as opposed to 6.7 grams for plain "Vacuosa."

As a pilot test, 2 heaping teaspoonfuls of the "Vacuosa"-barium Pelloids were given to 9 fasting volunteers at 8 A.M. Abdominal x-ray films were taken at ½ hour intervals for 5 successive times on two of the subjects, and at hourly intervals for 3 hours on the other seven subjects. It was found that disintegration of the Pelloids was uniformly complete after the third hour, as judged by the change from small, discrete shadows to large, diffuse ones.

Another series of 10 cases was studied using the method outlined in the pilot test, except that films were taken at 1, 3, 8 and 24 hour intervals. None of the individuals had the laxative habit. Six were men, four women. They all had white collar jobs. Two typical examples of the results are shown in the left columns of Figures 1 and 2. In both these cases the pellet aspect of the "Vacuosa"-barium is still apparent in the three hour films. The 24 hour films reveal the thoroughness with which the carob gum preparation mixes with the feces in the large bowel.

In order to gain perspective for judging the in-vivo behavior of "Vacuosa," parallel x-ray studies were made using mixtures of psyllium seed gum with barium and karaya gum with barium, prepared exactly like the "Vacuosa"-barium mixture. The same 10 subjects were chosen so that results would be comparable. Figures 1 and 2 present all the films for 2 of these cases. The large mass of data obtained from the entire series is depicted graphically in Figure 3. The films for each case were plotted in the manner shown, and then the averages were taken for the composite picture. It will be seen that the carob gum preparation was the slowest to disintegrate and the slowest to pass through the gastrointestinal tract. The psyllium and karaya gums behaved alike, though the latter showed somewhat faster progress through the intestinal tract.

Laboratory and clinical observations were made on the effects of "Vacuosa" upon the stools of 17 hospitalized patients. Six of this group suffered from chronic constipation and two, from recurrent diarrhea. The remaining nine patients were considered to have normal bowel habits. The oral dose was 2 heaping teaspoonfuls of the Pelloids with 2 glasses of water taken at bedtime. Five consecutive stool examinations were made as regularly as possible, both before and during the administration of "Vacuosa." Each specimen was weighed and measured volumetrically. The gross physical properties were carefully noted. The stools passed during the period of medication were submitted to microscopic examination as well.

Since this series is small, only the total figures are indicated.

TABLE I

	CONTROL	"VACUOSA"
Number of stools	56	47
Total weight of stools	9,167 Gm.	8,457 Gm.
Total volume of stools	9,935 cc.	10,154 cc.
Average weight	174.87 Gm.	193.34 Gm.
Average volume	185.40 cc.	225.34 cc.

In seven stools "Vacuosa" Pelloids were definitely identified grossly; and in fifteen, microscopically. There was an average gain of about 20 grams per stool, or 10.2 per cent, as shown in Table I. The stool bulk increase averaged about 40 cc. per unit, or 22.0 per cent, after "Vacuosa." The stool containing carob gum tended to be soft, gelatinous and homogeneous, while its control counterpart was either hard and formed or loose and mushy. Liquid stools were not altered by this preparation. The typical "Vacuosa" stool had such consistency that it did not settle out when placed in a container but maintained for hours the shape in which it was passed. The stool mass was characterized by a mucilaginous coating on its surface which often revealed tiny gelatinous particles resembling fine tapioca pudding. These particles under the microscope were seen to be remnants of the "Vacuosa" Pelloids.

In addition to the 44 patients mentioned above, "Vacuosa" was given to 12 private ambulatory patients with chronic constipation. Some patients of this latter group have taken "Vacuosa" regularly for 2 years. It has been interesting to note that the majority of the normals and the constipated alike, volunteer the comment that their stools become "easier to pass" and none experienced epigastric distress or abdominal colic after taking "Vacuosa." The full benefits of "Vacuosa" may not be obtained, however, until treatment has been in progress for several days.

DISCUSSION

Both the x-ray studies and the stool examinations have indicated that the colloidal gel resulting from the disintegration of the "Vacuosa" Pelloids permeates the fecal mass in the colon and mixes thoroughly with it. The greatest effect on the feces is the alteration in consistency. There is little actual increase in stool weight.

The comparative x-ray studies of carob, psyllium and karaya gums illustrate the important fact that carob gum does not disintegrate into a gelatinous state until it reaches the large bowel whereas the other two gums are transformed much more quickly and at a higher level of the gastrointestinal tract. Subsequent clinical observations indicate that there is no interference with normal digestion and less sense of bloating or distention with the use of carob gum preparations than the others. This may well be due to the fact that carob gum Pelloids maintain their integrity through the small bowel and do not increase the rate of peristalsis and the rate of passage, alterations which frequently result from the rapid swelling seen with other gums.

No instance of any allergic reaction attributable to "Vacuosa" has been experienced. Sensitivity to other vegetable gums has been reported by Gelfand (2). "Vacuosa" Pelloids have ready patient acceptability and are easy to swallow.

SUMMARY

1. The physical properties of carob seed gum are discussed.

2. A study of the behavior of this gum in the gastrointestinal tracts of human beings is described.

a) Twelve attempts were made by x-ray to demonstrate increased colonic contents 12 hours after volunteers took 2 heaping teaspoonfuls of "Vacuosa" orally.

COMPARISON OF VARIOUS GUMS AFTER INGESTION

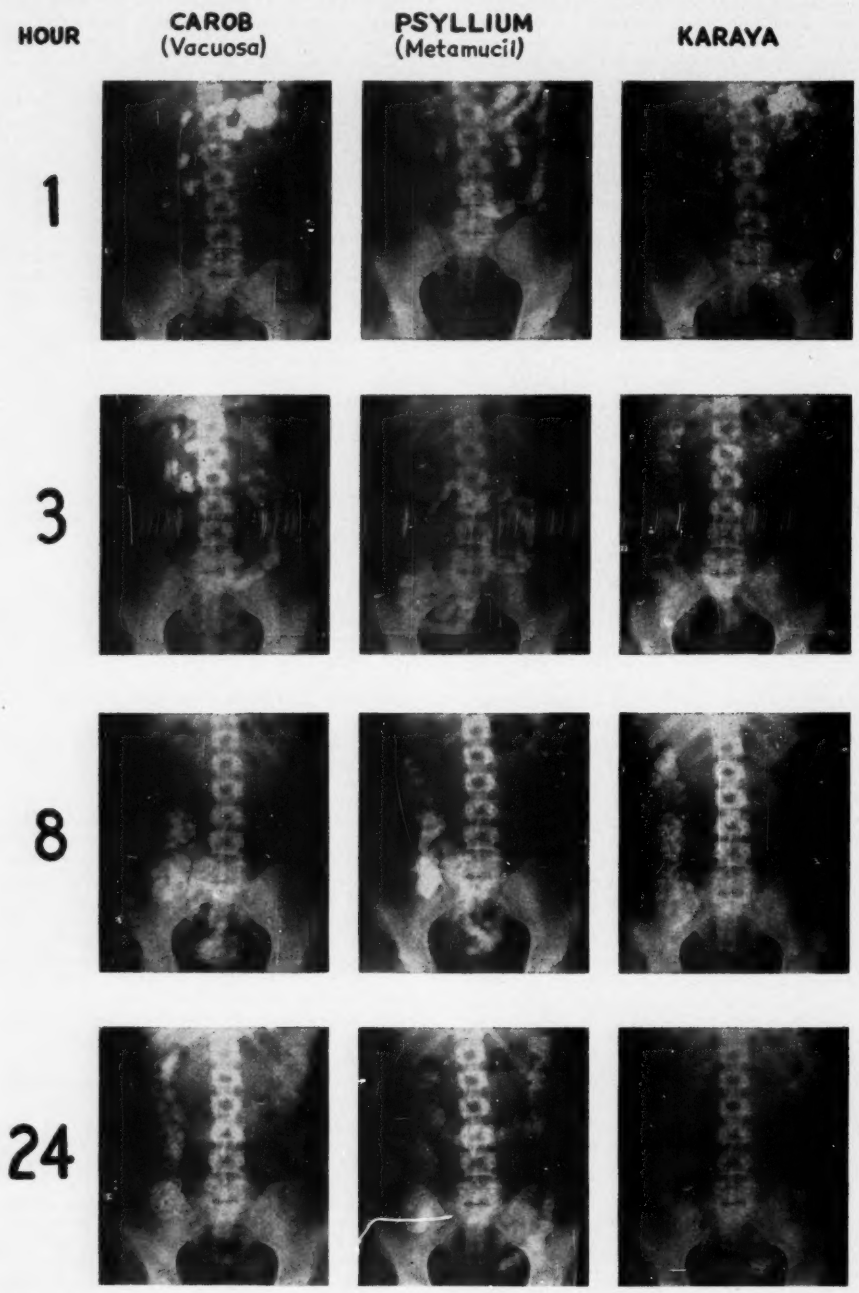


Fig. 1 Patient F.M. Note difference in rate of passage and disintegration.

Comparison of Various Gums After Ingestion

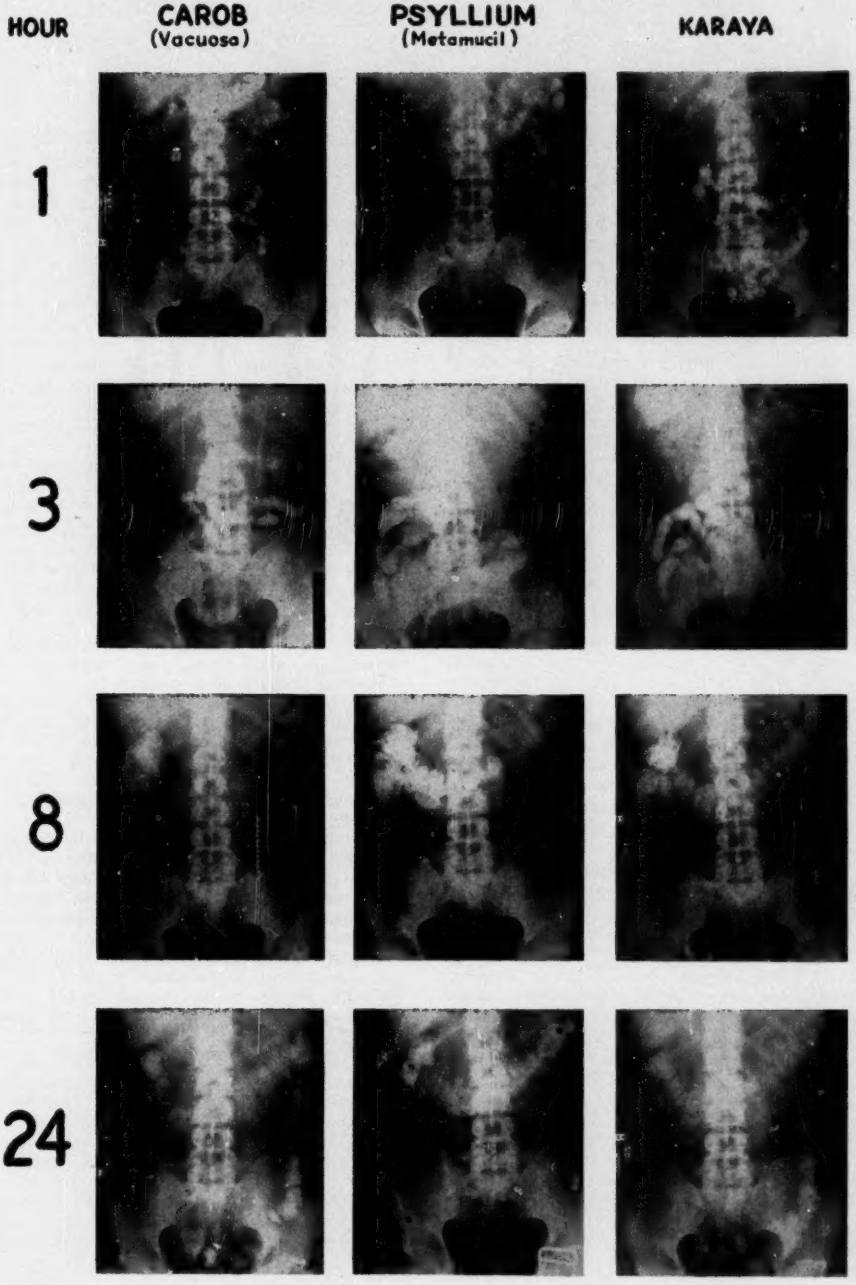


Fig.2 Patient R.L. Note difference in rate of passage and disintegration.

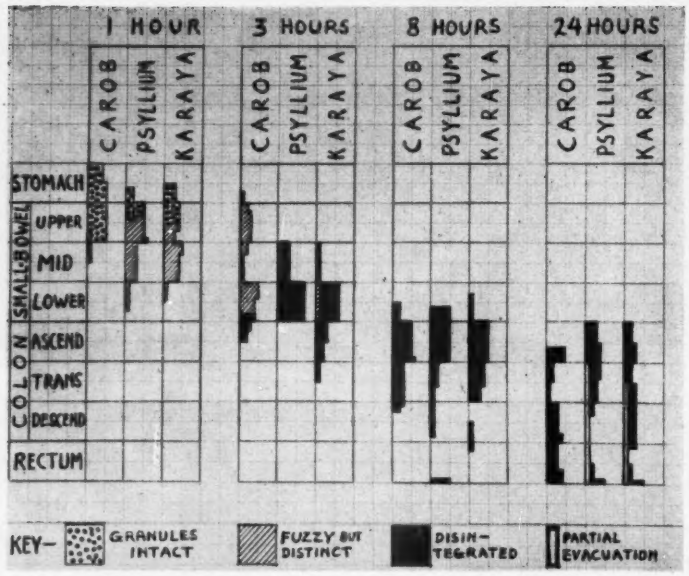


Fig. 3. A graphic representation of the results of x-ray studies made on 10 individuals who took 3 special gum preparations by mouth.

b) The progress of "Vacuosa"-barium Pelloids ingested by 19 subjects was followed from stomach to rectum by x-rays with special reference to position and time of disintegration.

c) Ten members of this group were similarly studied twice again, using psyllium gum-barium and karaya gum-barium mixtures. The x-rays of 2 cases and a chart of the average results are presented.

d) The quantitative and qualitative effects of "Vacuosa" upon the stools of 17 hospitalized patients are reported.

3. A brief discussion is given concerning the advantageous features of "Vacuosa," which encourage its further clinical use.

Conclusions

1. The swelling capacity of carob gum in a neutral or alkaline solution to more than 7 times its original volume has been demonstrable in vitro.

2. "Vacuosa"-barium Pelloids observed serially by x-ray after ingestion by normal individuals were seen to maintain their identity for the first 3 hours in the stomach and small bowel. The disintegration time for "Vacuosa" Pelloids approximated the ideal physiological timing in that they did not reach their maximal colloidal mass until they were in the colon, whereas psyllium gum-barium and karaya gum-barium Pelloids disintegrated much sooner and passed more rapidly through the upper gastrointestinal tract. In the colon and rectum, however, all gums appeared to behave similarly.

3. "Vacuosa" is an acceptable, bland, non-allergenic substance with the capacity of forming a colloidal gel which clinically affects stools in a way which makes them "easier to pass" and assists in promoting normal stool habits by causing an increase in bulk which is soft, homogeneous and non-irritating.

Footnote. X-rays produced in Figures 1 and 2 were taken at Columbia Hospital, Milwaukee.

References

1. Badosa, J., Serrallach, J. A., and Monroset, I: La Hemicelulosa de Semilla de Algarrobo como Laxante Mucilaginoso, Med. Espanola, 18:55 (July) 1947.
2. Gelfand, H. H.: The Vegetable Gums by Ingestion in the Etiology of Allergic Disorders, J. Allergy 20:311 (Sept.) 1949.

CHRONIC INVOLVEMENT OF THE LIVER IN INTESTINAL AMOEBIASIS. (CHRONIC AMOEBIC HEPATITIS)

RAPHAEL SANDLER, M.D. (BERLIN, D.T.M.&H. (LONDON) Tel-Aviv, Israel.

INVOLVEMENT OF THE LIVER (hepatic amoebiasis) is the most frequent complication of intestinal amoebiasis. Generally, only amoebic abscess of the liver is mentioned, less frequently acute amoebic hepatitis, mostly as precursor to abscess formation. Chronic amoebic hepatitis or chronic involvement of the liver, in patients suffering from chronic intestinal amoebic infection, without signs of abscess formation, is almost never considered, as if it were non-existent.

In searching the vast literature on amoebiasis I could find but very little on the chronic variety of amoebic hepatitis. Generally, authors, if at all, mention chronic hepatitis only incidentally. Of all these I want to cite the following authors: Castellani (1944) demonstrated three clinical signs pointing to an enlargement of the liver in cases of asymptomatic amoebic hepatitis. He thinks that this enlargement is caused by amoebic infection. There was no fever, no leucocytosis, neither was the liver palable. Sodeman & Lewis (1935) have written the most important paper on this subject stressing the importance of awareness of the possible occurrence of hepatic amoebiasis, especially its early recognition. However, they do not deal with the subject of chronic amoebic hepatitis. Only Payne in India and Fischl in Palestine deal specifically with chronic amoebic hepatitis. To the last three papers I shall make further reference.

As the symptoms of chronic amoebic hepatitis are often slight and therefore do not arouse suspicion, the condition is usually not noticed at all, and certainly its etiology not suspected. Diagnosis will often come too late for early prevention and therapy. What will happen to those cases which never become acute? Sodeman & Lewis write: "Amoebic hepatic disease is important often long before pus is available and we must depend upon findings less diagnostic than the ideal or sit back and wait until the disease has progressed to the advanced stages mentioned above." For the sake of early diagnosis we must try to elucidate the character and symptomatology of this condition, which, in my opinion, occurs very often in the course of chronic intestinal amoebic infection, representing the most important complication of the intestinal process.

INCIDENCE

The true incidence of liver involvement in amoebiasis is impossible to ascertain. The published incidences vary widely. As it is probable that in every case of intestinal amoebiasis amoebae are swept by the portal stream into the liver, every patient may at some time show symptoms pointing to the liver. Such symptoms, although vague and passing quickly, are often found. In this series I shall consider only those showing distinct and distressing symptoms and signs over a considerable period. The saying of an authority like Faust: "Amoebic infection of the liver is probably much more common than the records of acute amoebic hepatitis indicate," points to the possibility that a great many cases are missed. Payne, indeed found among 1000 cases of amoebiasis in India 50% of mild hepatitis, 3.9% of acute hepatitis and 2.8% abscess. He remarks: "Hepatitis was so common as to become part of the disease." Though 50% is rather a high figure it seems probable as the patients concerned were military personnel who were under constant observation, and thus transient disturbances could be detected immediately. This series of 47 cases of amoebic hepatitis belonged to 180 cases of amoebiasis, seen by the author in the last four years, i.e., an incidence of 26%. This figure, however, cannot be relied upon too much because no exact degree of severity of symptoms can be stated for introducing cases into this series. The patients were all Jewish workers and clerks from settlements in the south of Israel.

Sick fund of the General Jewish Workers' Organization.

PATHOLOGY

The term "chronic involvement of the liver" is best used here, because the incidental process is not yet well understood. The term "hepatitis" is generally employed for very diferent sorts of non suppurative damage to the liver parenchyma (i.e. of toxic, trophic, obstructive or vascular origin.) Often it is spoken of as "hepatic abscess" when there is no reason at all to suspect the presence of an abscess. The term "chronic abscess" is used too, in cases in which symptoms are not very significant.

The purpose of this investigation must be, firstly, to elucidate the cause of the liver disturbances, secondly, to learn the pathologic changes produced by the agent. The liver process is without doubt produced in a great many cases by the presence of the amoebae in the liver where they had been swept by the way of the portal vein. There, they may, by their lysins, give rise to destruction of liver tissue, or after having been destroyed, exert a toxic action by their disintegration products. (Intrahepatic influence). The liver process may also be a purely toxic phenomenon through toxins absorbed into the blood stream produced by the amoebae in the wall of the intestines, or toxins produced by bacteria which secondarily invaded amoebic ulcers. (Extrahepatic influence). It is thought probable that in every case of amoebic infection of the intestines amoebae are swept into the liver. What usually happens to them there, is not known. The only histologic investigation of the primary lesion of amoebic invasion into the liver has been undertaken by Palmer (1938). He writes that "since the excellent work of Councilman & Lafleur in 1891 little has been written concerning the process of formation of early amoebic abscesses of the liver. This is surprising because of the relative high incidence of this complication." And "little attention has been given to the changes in the

liver outside the immediate sphere of influence of an amoebic abscess or to the changes found in the liver in the presence of active amoebic intestinal lesions with no definitive abscess formation." Councilman & Lafleur have already described the early amoebic lesion in the interlobular tissue about the portal vein, which according to them grossly resembles miliary tubercles. They stressed that because of the absence of inflammatory reaction no true abscesses are found. Palmer found in 18 of 19 cases of liver involvement (13 had abscess) an increase in portal connective tissues, in 10 a noticeable increase of lymphocytes and monocytes in the portal triads. In 9 there were fatty changes midway between ventral vein and portal triad. Very early abscesses begin as areas of lysis in the portal triad extending from there into the liver parenchyma. Around areas of liquefaction a thin meshwork of fibrinous strands is formed in which a moderate number of lymphocytes and monocytes, but no leukocytes, are found. The sinusoids in the neighborhood are moderately engorged with red blood corpuscles. Numerous patches of fibroses are found, perhaps from small abscesses which healed. These are often present at the time of active amoebic lesions in the intestine, without any abscess formation. Palmer states that definite hepatitis is always associated with active amoebic lesions in the colon. As to the cases without abscess, in 4 the liver was of normal size, in 1 small, and only in 1 enlarged.

Craig notes too that small fibrous areas are sometimes seen in livers of patients who have died of amoebic dysentery, which had not resulted in abscess formation.

The findings of Palmer conform with the clinical pathology of amoebic hepatitis. Although most authors think it possible that the intestinal process may have disappeared at the time of the appearance of the process in the liver, I was able to find in every case signs of active intestinal lesions. An active amoebic process in the intestines is apparently necessary for the maintenance of the hepatic process. The amoebae swept into the liver will be mostly destroyed and the lesions produced in the liver heal entirely. According to Rogers most amoebae degenerate before they can escape the vessel walls. This gives rise to congestion of the liver, which state was called by Rogers "presuppurative amoebic hepatitis." Craig speaks of the well-known but unexplained immunity of the liver. He says that it is impossible to believe that amoebae do not frequently reach the liver through the portal circulation. In spite of that the number of abscesses is very small. Napier is of the opinion that small "showers" of amoebae cause a minor degree of hepatitis which might well be overcome by the natural tissue resistance of an undamaged liver.

In chronic hepatitis constant invasion and reaction by the liver may lead to a long drawn fight which often only after years may be decided in favor of the liver, because abscess formation is seen very seldom as sequelae of amoebic hepatitis. This fight may not at all times give rise to clinical symptoms. Sometimes there are acute periods which, however, pass without any treatment. Between these periods the chronic process goes on. This conception makes it also probable that *Entamoeba Histolytica* will be found in a greater percentage of hepatic complications, if carefully looked for. The dependence of the liver condition on the intestinal process is also shown by the observation that the liver condition improved definitely and permanently only when the intestinal symptoms disappeared, after antiamoebic treatment of the intestinal process. That means that from now on no amoebae could reach the liver.

As amoebae have never been found in the lesions described, there remains the other possibility that the changes seen are induced by toxins produced by amoebae or bacteria in the wall of the intestines, or that this influence may be active in many cases where hepatic tenderness is met. This tenderness shows that a great part of the liver must be involved, due to the widespread occurrence of the above described lesions, or swelling of the whole liver, solely of toxic origin. As to the possibility of a secondary invasion of bacteria by way of amoebic ulcers, Acton's view may be cited that in certain cases bacterial emboli from the intestines may cause symptoms of hepatitis. Heilig & Vivesvar point out that a discrepancy exists between the fact that *Entamoeba Histolytica* produces no toxin, in any case no known toxin, and the clinical impression that many patients suffering from chronic amoebiasis, look and behave as if they were toxic. Their symptoms, e.g. emaciation, sallow complexion, hyperirritability, closely resemble the symptomatology of hepatic insufficiency at a time when there is no clinical hepatitis. These symptoms disappear, according to these authors, under the influence of emetine. They undertake to show with the help of the hippuric acid test that there exists a definite liver damage in a great percentage of cases of amoebic dysentery. They do not think, however, that the toxins which cause this damage are produced by the amoebae. According to their opinion they are produced by the bacterial flora, to which the amoebae open the way into the tissues. As a proof of this opinion they state that they found that liver function is less affected in amoebic hepatitis. In any case they found that liver function tests are rarely of help in early amoebic hepatitis. The authors themselves acknowledge that in India many toxic factors are at work which may diminish liver efficiency.

The effect of emetine does not give us any clue as to the presence or absence of amoebae in the liver. The question if there exist special predisposing causes which may explain the failure of the liver to dispose of the intruding amoebae, is not easy to answer. I was not able to find any difference as to antecedent liver illnesses or the nutritive status, between those suffering from liver complications and those without.

CLINICAL SYMPTOMS AND SIGNS

The outstanding symptom of chronic amoebic hepatitis is the tenderness of the liver. However, most patients do not complain spontaneously of pains in the liver region. It is only during palpation of the abdomen that tenderness is detected. Distinct painfulness over the whole area of the liver is elicited by fist percussion. Only very distinctly painful livers were, however, considered, minor grades—which of course were seen more often—being excluded, although these too must be taken as a sign of liver involvement. Often only a circumscribed area of the right chest (the one

lying between the anterior and posterior axillary line) was found to be painful. Pain on palpation of the lower margin of the liver is usually not sharp enough for distinguishing it from the pain felt also by the normal liver when palpated on deep inspiration. Subcostal tenderness was found by Klatskin to be the most frequent abnormality observed. He elicited tenderness by compressing the lower chest anterior-posteriorly between the palms of the hands. (Compression-tenderness.) It proved of great help in differential diagnosis. Enlargement of the liver is usually minimal. As minor enlargement is difficult to assess, this sign is not of much usefulness in the diagnosis of chronic amoebic hepatitis. In 29 out of 44 cases the liver could easily be palpated, but only in 11 it was found enlarged by at least two fingerbreadths below the costal margin. It should be noted that 6 of these were Yemenite Jews in whom also other intestinal parasites might have been responsible for the liver enlargement, as the latter is often found amongst them. Pain in the right shoulder was elicited only in 8 patients, all of them belonging to the graver, more protracted cases. Pain in the left shoulder was never found. Spontaneous pains were often found to be dependent on the position of the body. 8 patients could not lie on their right side without experiencing pain, while 4—on the contrary—felt pains in the liver region when lying on the left side. Pain in the upper back was complained of by 8 only. Pain elicited by sharp movements, as e.g. bending down, as described also by Rachmilewitz was complained of by 7. 2 felt pains on deep inspiration. It is to be understood that all the symptoms and signs are of course less distinct in these chronic cases than in cases of acute inflammation or abscess formation. Enlargement of the spleen was never seen, except in one of the acuter cases. Mostly, patients complained only of heaviness in the right epigastrium, especially after heavy meals. Dyspeptic symptoms which do not belong to the symptoms of uncomplicated intestinal amoebiasis are found very often in cases of liver involvement, leading the suspicion to the liver. 20 complained spontaneously of loss of appetite, 19 experienced nausea, 11 had vomited occasionally, 11 had a distinctly coated tongue, only 4 complained incessantly of a bad taste, and 4 of heartburn.

Constitutional symptoms, like general malaise, weakness, fatigue, nervousness, loss of sleep and headache may be attributed to the primary disease as well as to its complications in the liver.

33 patients had had diarrhea, 21 constipation, 24 suffered from gaseous distention. As pointed out above, it is of much interest to note that a large part of these suffered from intestinal symptoms at the time of the liver disease, pointing to an active process in the intestines, at the same time. This is also manifested by the finding of *Entamoeba histolytica* in the stools in 33 cases. Jaundice, even latent, was not found except in cases 1, 3, 5. This is a known fact, and, indeed, one is justified in stating that the presence of jaundice suggests a cause other than amoebic invasion for the liver disease.

This state of affairs continued characteristically for months, without interruption, mostly with only slight variations in intensity. Acute relapsing attacks with intervals of relative wellbeing occurred only in 2 patients, and these were accompanied by small elevations of temperature (cases 5 and 6.). Except in two other cases (1, 7) fever was not encountered. Perhaps small exacerbations of pains were sometimes accompanied by subfebrile temperatures, but these were apparently too insignificant to be noticed by the patient. This conforms with the statement of Rachmilewitz, that the longer the cases are drawn out the greater the tendency for the temperature to become subfebrile. Roger says: "Fever is often insufficient to attract attention." Besides the patient with the acute exacerbations no one was confined to bed, although the working capacity was often rather considerably restricted. Some felt worse in summer, but most did not experience any changes in the different seasons of the year.

To summarize: We find a picture of ill health, rather incapacitating, dragging on for a long time, eventually ending in complete recovery. To the syndrome of chronic intestinal amoebiasis there is added an epigastric syndrome pointing to an involvement of the liver. The manifestations of the liver disease vary according to the acuteness of the process. The main feature is the tenderness of the liver elicited by fist percussion, in acuter cases also pains in the liver region on movement. Jaundice is hardly ever to be found. The characteristic features of amoebic hepatic abscess and acute amoebic hepatitis, such as high fever, grave pains, changes in the X-Ray, etc., are not to be found in chronic amoebic hepatitis.

ROENTGEN-DIAGNOSIS

Signs of involvement of the right lung or limitation of movement of the right diaphragm were detected in only one case (case 1) on clinical as well as x-ray examination, and in a second (case 6) on x-ray examination only. This finding is understandable in view of the character of the lesion of chronic amoebic hepatitis, which is not likely to lead to an extension of the process to the neighbouring organs. Sodeman & Lewis detected no changes in the x-ray in 18 of 33 cases of acute amoebic hepatitis. With development of abscess 86% were found positive. In hepatitis there was never evidence of bulging or extension, but only elevation and impaired movement of the diaphragm. They state that x-ray is the more often found positive the more advanced the process is. Pulmonary signs, could be detected by them in 3 cases only.

DIAGNOSIS

Which criteria are necessary and sufficient for establishing the diagnosis of amoebic hepatitis? Absolute certainty is given only by the demonstration of *Entamoeba histolytica* in the liver. However, these, of course, will be found only by biopsy. Another sign which is considered by most authors as pathognomonic, the anchovy—or chocolate sauce "pus," probably does not develop in amoebic hepatitis. If we should wait for it to develop, we should miss the more hopeful treatment at an early stage, and especially, in all those cases which never reach the stage of abscess formation, but cause longstanding invalidism, and are far more numerous.

As in any other disease we must try to come to an early diagnosis, but in this condition—as Sodeman & Lewis have pointed out—the absolute criteria for di-

agnosis are always absent. This is the more correct the more chronic the process.

Therefore, in chronic amoebic hepatitis we shall have to rely on findings which can only be suggestive for the diagnosis, but must nevertheless be taken as sufficient for the institution of specific treatment. The clinical symptoms, as shown above, are vague, but point objectively to an involvement of the liver, besides a chronic process of the colon. This combination itself must arouse suspicion. In most cases in which liver disease was met together with an intestinal process and where other diseases could be ruled out, *Entamoeba histolytica* or a positive Complement Fixation Test was found. The finding of Entamoeba histolytica in the feces is of course not confirmatory, but in many cases establishes the presence in the body of the originator of the infection. The same is true for the Complement Fixation Reaction which often helped us to strengthen our suspicion when *Entamoeba histolytica* could not be detected.

In any case, if a chronic enlargement and/or tender liver is found, the suspicion of its amoebic origin should be aroused, and symptoms from the intestines be looked for. If *Entamoeba histolytica* is found in the stools or the Complement Fixation Test found positive, these findings should, in the absence of any other suspicion for all practical purposes, lead to the provisional diagnosis of amoebic hepatitis and the institution of antiamoebic treatment.

The application of emetine injections as a therapeutic test for the diagnosis of amoebic hepatitis is of no use in chronic amoebic hepatitis.

LABORATORY DIAGNOSIS

Stools: In 34 of 47 cases (72%) *Entamoeba histolytica* was found, in the free form or encysted. In every case it was sought for many times, and examined in saline and Iodine, after Magn. sulf. had been taken. In 8 cases it was found by culture. 72% is a rather high percentage in comparison to most series of acute amoebic hepatitis or amoebic abscess. Figures given are mostly low from 30% upwards, only in few reports they are higher (70%-Berne.) As shown in the chapter on the pathology of chronic amoebic hepatitis the high percentage of positive stools is important for the understanding of the process. If the presence of *Entamoeba histolytica* in the colon is necessary for the smouldering on of the hepatic process, then, in all cases eventually *Entamoeba histolytica* should be found. This seems to me to be the case, if only enough and thorough examinations are made. In one case who suffered from chronic hepatitis with acute exacerbations, Entamoeba histolytica was found, after many previous negative examinations, the first time several months after the acute symptoms had subsided.

The Complement Fixation Test is widely used by us, since it has been introduced in Israel by Prof. Klopstock. I think it is useful, especially in certain cases of chronic hepatitis where symptoms from the bowels are not conspicuous enough to suggest the amoebic origin of the liver disease. Very often it showed us the right etiology long before a positive stool could confirm the diagnosis. In 25 of my cases in this series it was done and found positive in 20. It is probable that if repeated examinations had been made on the residual 5, they would have been positive too. The test was repeated several times after treatment.

Urine: An increase in urobilinogen excretion (++) was only found in 2 cases besides traces of bilirubin, during the most acute stage, reverting quickly to normal after emetine injections. The negative finding of bile pigment in the urine is a known fact, also in cases of amoebic liver abscess. It may even be said that a positive finding should make us suspicious of the diagnosis. It is known that even extensive involvement of the liver need not lead to disturbance of the excretion of bile, but the consistent negative finding is in any case a remarkable fact.

Blood-Picture: As in most cases no suspicion of anemia was aroused, the red blood picture was examined in 11 cases only. A low colour index was found but in one case (60% Hb., Er. 4, 5 M, C.I.O., 66) at the time of attacks of strong pains. Under specific treatment and iron, hemoglobin increased slowly, and at the same time the attacks subsided. No other cause for the hypochromic anemia could be elicited. A slight leucocytosis was several times found at the time of more acute symptoms, subsiding together with these. The more acute the process the higher the leucocyte count will be. However, even in abscesses normal counts have been met with. A shift to the left of the leucocytes was never met with, not even at the time of acute exacerbations, when the total sum of leucocytes was increased. The polymorphs were often high, up to 82%, the lymphocytes low down to 15%. The cosinophils were found normal, except in 5 cases (more than 8%) who were all Yemenite Jews possibly harbouring other parasites too. The monocytes were increased only in 2 cases (10 resp. 16%), reverting after two months to 7%.

The Blood Sedimentation Rate was often accelerated, especially in the more acute cases, in others entirely normal. The finding of Nicoll & Simons that the B.S.R. is accelerated in ¾ of the cases of amoebic hepatitis, may be applied to acute cases only. Berne recommends the B.S.R. as an aid in measuring the activity of the infection and as indicator for the need of further treatment. As, however, the B.S.R. may be normal in chronic amoebic hepatitis, this finding should not prevent us from treating these cases.

The Weltmann coagulation Band was slightly lengthened in 5 out of 13 patients, twice 8 and three times 7½, reverting after some time to normal in 3 cases in which it was repeated. In 2 cases it was 5, in 1 of them at the time of pulmonary involvement.

Liver Function Tests: Examinations of liver function in amoebic hepatitis, acute and chronic, have only been undertaken by Brown & Hodgson who employed the Bromsulfalein Test, by Heilig & Vivesar with the Hippuric acid test and Greig with the Levulose Test. Liver function tests were performed by me in the hope that their results would furnish an objective proof of liver involvement and perhaps also some indication as to the nature of the process. As a disturbance of one or the other tests is met only with a quite extensive and advanced disturbance of the liver, not too much can be expected from their employment. In spite of that, a composite picture of various functions, tested several times at various stages of the disease, should give us some sign of changes in the liver.

Of those tests showing early disturbances of the liver the Bromsulfalein tests has been found positive in 8 of 13 cases of liver abscess by Brown & Hodgson. It may be that this test which is of limited value in the presence of jaundice, and is also quite sensitive, will be of some help for the examination and follow up of chronic amoebic hepatitis. Unfortunately, I was not in the position to undertake this test for technical reasons. In its place I used the

Formalin Test: This test like the Bromsulfalein Test, is thought to point to interstitial damage. Out of the 6 cases in which it was performed it was positive in 5, in 3 cases++, in 2 ++++. In all of them it improved or became negative together with clinical improvement. Although the number of examinations done is small, this test which points to the seat of the pathological changes of amoebic hepatitis seems to be the most promising besides the Bromsulfalein Test.

Takata Ara Test: This test was done in 13 cases and found positive in 2 only. It was found positive several times, until it became negative after nine months. As this test is not very sensitive a negative finding does not imply that there is no liver damage.

Cephalin Test: This test is a very sensitive indicator of active disturbances of the liver parenchyma. Its repeated examination is of prognostic significance, and it is said that the speed and degree of flocculation agrees closely with clinical observation (Dick). It, therefore, seemed to be of value to use it here. In 4 out of 8 cases in which it was done it was found positive, but only in one stronger than one plus, together with a positive Takata Ara Test, a positive Formalin Test, and a lengthened Weltmann Band. The three other cases were also positive at the same time as a positive For-

malin Test and became negative together with the latter. Although a one or two plus test is not considered significant the above facts should be noted.

The *Bilirubin* content of the plasma was found in 12 cases between 0.2 and 0.4 mg %, all of them giving the direct negative reaction, except 2 which at one time gave a weak direct reaction but soon became direct—negative.

TREATMENT

Amoebic hepatitis is known as that field of amoebic infection which is most strikingly influenced by emetine. Yet, in chronic amoebic hepatitis emetine does apparently not exert any great influence. This statement will be a great surprise for many, although some authors have mentioned it already. Craig says (in Tice's Practice of Medicine): "In chronic abscess in which amoebae are absent, emetine appears to be inefficient." It is not clear to me whether by "chronic abscess" the same process is meant as by chronic amoebic hepatitis, and whether it is sure that amoebae are absent in this condition. Fischl writes: "Everything helped: Emetine, Yatren, Spirocid (Acetarsone) and also no therapy." As his cases were mostly children this possibly conforms with my experience with three children in whom subacute liver symptoms disappeared entirely during a course of emetine. According to Payne emetine is often of no help in more severe forms of amoebic hepatitis or abscess even. Berne tells of a patient who, after liver drainage, deteriorated steadily with emetine injections, but improved rapidly with Yatren.

The great difficulty in judging the effect of emetine is shown by the fact, which has been commented upon by many authors, that an attack of amoebic hepatitis may subside by itself, so that the disappearance of symptoms at the time of emetine injections may be a mere coincidence. I have often seen acute attacks pass without any therapy.

Besides, it is known that emetine exerts even a striking effect also in other conditions of the liver, e.g., schistomiasis, fasciolasis and paragonimiasis (Brookfield). An unspecific sedative effect on the liver as well as on the bowel has been suggested too (Hennessey). Napier is of the opinion that the improvement caused by emetine in hepatic congestion, though suggestive, is not confirmatory, as this drug has a non-specific effect on hepatic congestion. E Melchior has used emetine in various pyogenic infections with good results. Also the fact that after large doses of emetine which is eliminated very slowly, hepatitis may develop, speaks against a striking specific influence. Priest (cited by Adams) says that "it is remarkable that even after much emetine or auremetine a patient may suddenly develop amoebic hepatitis and amoebic abscess" In my series, 10 patients had during the last three months before their present disturbances of the liver, been given 0.3—0.8 grammes of emetine. One woman had already undergone seven courses of it. Therefore, a positive influence should be viewed very critically and, in my opinion, one cannot decide on the amoebic origin of cases of acute or chronic hepatitis on the strength of a therapeutic test with emetine, as many authors do.

We know now that emetine does not eradicate the amoebic infection of the bowels, except perhaps in a small percentage (15% Craig). Emetine only influences the acute symptoms of amoebic dysentery and amoebic hepatitis. In 25 cases of my series 0.25—0.75 grammes of emetine, sometimes repeated courses, were given. With the exception of the more acute phases, only passing improvement of the clinical symptoms, such as pains, dyspepsia, general bad feeling, could be detected.

It seems to me that treatment can only be preventive. That means that the parasite must be attacked in the intestines and eradicated there. Thus it will be prevented from reaching the liver and carrying on the process there. In this connection it is interesting that De Silva attributes the increase in the number of cases of amoebic hepatitis to incomplete treatment of amoebic dysentery. The above mentioned case of Berne which improved with Yatren demonstrates the importance of treatment of the colonic process, especially in cases resistant to emetine. Berne found also that the mortality of amoebic hepatic abscess was higher with active colonic disease than with latent colonic infection. This indicates the need of active colon therapy Berne recommends the treatment of the colon as part of the program to prevent reactivation of an old hepatic abscess. He cites instances of patients who had had abscess several years ago, which may mean a new liver infection, or a reactivation of an old hepatic process. Many of our patients had also had acute disturbances of the liver some time ago, which had subsided after treatment or without it.

Thus, everyone of our patients was given Yatren alone (28 grammes in 14 days) or 14 grammes in 7 days) followed by Acetarsone (5 grammes in 10 days). At the beginning I feared the use of these Arsenic preparations in cases of liver diseases, but used it later on in cases in which Yatren did not seem to suffice, as at that time we had no other antiamoebic drug at our disposal. According to Lichtman, Carbarsone like the other pentavalent Arsenicals (Acetarsone, Tryparsamide) is surprisingly non-toxic to the liver. As Carbarsone is a very effective drug for the eradication of the amoebic infection from the bowel, it may be used in cases of chronic amoebic hepatitis in order to prevent further invasion of the liver. I did not see any impairment of liver function; on the contrary, the use of Carbarsone seemed to influence the liver process favorably.

The institution of a suitable dietary regimen exerted a good influence on the liver condition. The patients were advised not to take any alcohol, as little fat as possible, with the exception of some butter and milk, free amounts of carbohydrates and large amounts of proteins, of animal and vegetable origin. As the cost of commercial protein- and aminoacid- preparations was prohibitive they were advised to take considerable amounts of white cheese and sour milk, both made from skimmed milk. They were given small meals frequently. The patients were told that ample nutrition was more important than an occasional dietary fault which was followed by some intestinal upset. Most patients had for some time followed a strict dietary regimen. On the regimen described they soon felt much better. I am sure that this, as in intestinal amoebiasis, is a very important part of the therapy.

Heat applied to the abdomen and to the liver is a very important and agreeable adjunct to the therapy.

General rest, i.e. lying in bed during the more acute disturbances and abstaining from all manual work, if possible, is very effective, although not immediately after more acute periods. The importance of prolonged rest after liver illnesses, as long as there are still signs of activity of the process, has recently been greatly stressed by various authors.

Most of the cases of this series were followed up for years. In none of them did abscess develop. During these years I saw but a single case of amoebic liver abscess. It seems that the chronic process in the liver slowly dies down and eventually heals entirely. I want to add the following observation which may be of interest: I have noticed in a series of 58 cases of chronic amoebiasis that many of those cases, the intestinal condition of which did not improve for years, suffered from chronic hepatic involvement. It appears that the hepatic process on its part exerts some influence which impedes improvement of the intestinal infection. It may be that the liver factor of Faust is missing here.

SUMMARY

Of the various stages of hepatic amoebiasis generally only abscess formation is described, much more seldom acute hepatitis, mostly as precursor of abscess formation. Chronic amoebic hepatitis is mentioned very seldom although it is the most frequent complication of chronic intestinal amoebiasis. Payne found it in 50% of his cases of chronic amoebiasis, in this series 26% suffered from chronic liver involvement. The pathology of this condition is not yet well understood. The question is whether the presence of amoebae in the liver is essential or whether some toxic influence suffices to induce the pathologic changes. Some investigations on the histologic changes in the absence of abscess or outside the immediate sphere of abscess, have been made by Palmer (1938) and much earlier by Councilman & Lafleur (1891). They found an increase in portal connective tissue with infiltration of lymphocytes and monocytes, with no involvement of the parenchyma, besides some congestion. Numerous patches of these fibrotic areas were found at the same time as active amoebic lesions in the intestines. It seems probable that by constant invasion of amoebae from an active intestinal process the above described reaction on the side of the liver is carried on, the invading amoebae soon being destroyed (Rogers). This conception is strengthened by the great percentage (72%) of Entamoeba histolytica found in the stools in this series, and the presence, at the same time, of clinical symptoms of an active intestinal process, the liver condition improving together with the intestinal symptoms after treatment of the latter.

The symptomatology is characterized by the chronicity of the process. Therefore, many features of the acute phase of hepatitis, such as fever, severe pains, enlargement of the liver, are not present, or only in a minor degree. The main feature is the tenderness of the liver. Constitutional symptoms are much more outstanding than in chronic amoebiasis, presenting the picture of early liver disease. The x-ray is mostly negative.

As we must try to come to an early diagnosis, we cannot afford to wait for the absolute signs of the developed disease to appear. Therefore, we must rely upon suggestive findings, e.g., the clinical picture of the liver plus intestinal disease, the finding of *Entamoeba histolytica* in the stools, and/or a positive Complement Fixation Test. This test was found positive in 20 of the 25 cases in which it was performed. The failure to find bile pigments in the urine is an important suggestive point. No shift to the left is found in the differential blood picture, even with leucocytosis. The blood sedimentation rate tends to become normal the more chronic the process. Various liver function tests, performed several times during the course of the disease, gave some indication of the character of the process.

Emetine has no conspicuous effect in the chronic form of amoebic hepatitis. The treatment of chronic amoebic hepatitis is mainly preventive, i.e. the intestinal process should be treated to avoid the liver being further invaded by amoebae. This therapy together with proper nutrition gave good results.

REFERENCES

1. Adams, Transactions Roy. Soc. Trop. Md. & Hyg., Vol. 38, 237 (March) 1945.
2. Ash and Spitz, W. B. Saunders Co., Philad. & Sidney 1945.
3. Barker M. H., Capps R. B., Allen F. W., Jour. Am. Med. Ass., Vol. 128, No. 4, p. 997 (August) 1945.
4. Berne, Cl. L., Surg. Gyn. & Obstetr., Vol. 75, No. 2, p. 235 (August) 1942.
5. Brown P. W. and Hodgson C. H., Am. Journ. Med. Soc., Vol. 196, No. 3, p. 305 (September) 1938.
6. Canaan T. and Blohmer W., Archiv fuer Schiffs und Tropenhygiene, Vol. 44, p. 157, (April) 1940.
7. Cantor, Mosby, 1937.
8. Castellani Sir A., Rev. Gastroenterology, Vol. 7, No. 1, p. 1 (Jan.-Feb.) 1940.
9. Councilman and Lafleur, Johns Hopkins hosp. Rep., Vol. 11, p. 395. 1891 (Abstr. from Palmer s. No. 47).
10. Dick A., Brit. Med. Journ. 10. Febr. 1945.
11. Faust E. C., Rev. Gastroenterology, (May-June) 1941.
12. Faust E. C., La prensa Med. Argent., Sept., from International Med. Dig., (Febr.) 1945.
13. Fischl W. Harefuah, Vol. 12, No. 3. (March), in Hebrew 1937.
14. Greene, Arch. Int. Med., p. 356 (April) 1944.
15. Greig E. D. W., Trans Roy Soc. Trop. Med. & Hyg. Vol. 14. p. 207. 1940.
16. Heilig & Viviesvar S. K. Ind. Med. Gaz. Vol. 79, No. 8, (August) 1944 (frfom Trop. Dis. Bull. Feb. 1945).
17. Henessey R. S. W., Act. Med. Orient Vol. 4, No. 4, p. 103 (April) 1945.
18. Herrlich A., Abstr. from Trop. Dis. Bull. (March) 1944.
19. Hunman and Kampmeyer R. H. Am. Jour. Trop. Med. Vol. 17, No. 2, p. 263 (March) 1937.
20. Howell and Knoll, Am. Jour. Dis. Children, Vol. 61, p. 54 (Jan.) 1941.
21. Klatskin G. Ann. Int. Med. Vol. 25, No. 4, p. 601 (Oct.) 1946.
22. Lancet Editorial, p. 573, 28. Oct. 1944.
23. Lichtman, Diseases of the liver.
24. Lindskog G. S. and Walters W., Jour. Am. Med. Ass. Vol. 181, No. 2, p. 92, (11. Maj.) 1946.
25. Manson—Bahr P. Brit. Med. Jour. Vol. 2, p. 255 (23. Aug.) 1941.
26. Melchior E., Schweiz Med. Wochenschrift Vol. 76, p. 1054 (12. Oct.) 1946.
27. Munk I., from Trop. Dis. Bull., (Jan.) 1944.
28. Napier, The Macmillan Co., N. Y. p. 455, 1946.
29. Nicolle and Simons, from Trop. Dis. Bull. Nov. 1939.
30. Ochsner A. and de Bakey M., Surgery Vol. 13, p. 460 (March, p. 612), (April) 1943.
31. Ochsner A., and de Bakey M., Kleinsasse and de Bakey E., Rev. Gastroenterology. Vol. 9, No. 6, p. 438 (Nov.-Dec.) 1942.
32. Osburn H. S. from Trop. Dis. Bull.,(August) 1945.
33. Palmer R. B. Arch. Pathol. Vol. 25, p. 327. 1938.
34. Payne A. M. H., Lancet, Vol. 1, No. 7, p. 206 (17. Feb.) 1945.
35. Portis S. A. Journ., , Mount. Sin. Hosp. (May-June) 1943.
36. Rachmilewitz M. Act. Med. Orient. Vol. 3, No. 2, p. 35 (March-April) 1944.
37. Rappaport E. and Klatskin G., Ann. Int. Med. Vol. 14, No. 1, p. 17 (Jan.) 1947.
38. Rogers L., Lancet, Vol. 1, p. 463, 569, 677, 1922.
39. Rogers L., Churchill, London, 1939.
40. Sandler R., Am. Jour. Dig. Dis. Vol. 15, No. 4, p. 122, (April) 1948.
41. Sandler R., Am. Jour. Dig. Dis. Vol. 16, No. 7, p. 257 (July) 1949.
42. Sandler R., Harefuah. Vol. 37, No. 7, (2. Okt.) 1949.
43. de Silva S. Jour. Ceylon Branch Med. Ass. Vol. 41, No. 1, (April) 1945.
44. Sodeman W. A. and Lewis B. D. Am. Jour. Trop. Med. Vol. 25, No. 1, (Jan.) 1945.
45. Sodeman W. A. and Lewis B. D. Jour. Am. Med. Ass., Vol. 129, p. 99 (8. Sep.) 1945.
46. Teitelbaum et al., Int. Med. Ann. (May) 1945.

ANTACIDS AND AUREOMYCIN*

R. Greenspan, M. D., Helen MacLean, B. S., A. Milzer, Ph.D., M. D. and H. Necheles, M. D., Ph.D.,
Chicago, Ill.

WIDESPREAD CLINICAL USE of aureomycin has yielded good results in the therapy of a variety of infections previously difficult to treat or refractory to other antibiotics. Side reactions consisting of epigastric distress, nausea, vomiting and diarrhea are not uncommon, and, although usually minor in nature, they may become severe enough to interfere with, or even interrupt, treatment with the drug. It has been recommended by some that a preparation of aluminum hydroxide gel be prescribed along with the antibiotic (1-3), a procedure which is often effective in controlling gastro-intestinal upsets. However, it has been shown (3-6), that aluminum hydroxide gel (amphojel) significantly reduces the level of aureomycin in the serum when the gel had been administered together with the aureomycin, and it has been found that, in vitro, aureomycin is adsorbed by aluminum hydroxide gel (7). The gel is not absorbable, and, therefore, absorption of aureomycin from the intestine is diminished.

In our laboratory and hospital we have been interested in a new antacid: sodium carboxymethylcellulose (Carmethose).* We felt that it was advisable to determine whether or not this antacid affected the blood level of aureomycin, either by inactivation or by interference with absorption. For this reason in vitro tests were performed with aureomycin and amphojel or with aureomycin and carmethose, and tests were done on human subjects, comparing blood levels of aureomycin following its administration with and without an accompanying dose of either of the antacids.

Clinically, we have found carmethose to be an effective antacid which is able also to diminish or suppress the gastro-intestinal side effects of aureomycin. The latter experience is based on observations made on 15 patients and 10 normal subjects who were given aureomycin.**

METHODS

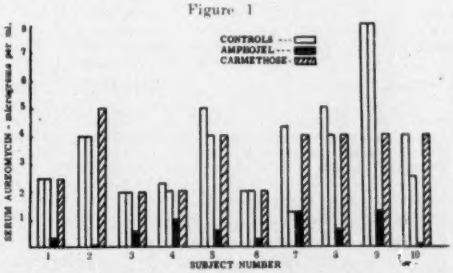
Normal male and female adults were used for this study. One single dose of aureomycin** was administered in the morning on a fasting stomach and a sample of blood was obtained under sterile conditions 5 to 6 hours later and refrigerated. In 7 of the subjects the dose of aureomycin was 750 mgm and in 3, the dose was 100 mgm. Forty-eight to 72 hours were allowed to elapse before the drug was administered again to avoid the possibility of a residual level (8). Two control levels were obtained on all subjects, after which carmethose liquid or amphojel liquid were given in 30 ml quantities 15 minutes before the aureomycin, and blood samples were collected as in the control tests. With two exceptions, aureomycin levels were run on the same day that the blood was drawn, and in those specimens held over, the serum was removed from the clot and kept frozen. Levels were determined with a serial tube dilution method routinely used in this laboratory for assaying antibiotics. The test organism was Bacillus #5 Dornbush.*** The culture was incubated in veal infusion broth for six hours at room temperature, diluted 1:10,000 with sterile saline solution, and 0.05 ml fractions were added to each of the graded serum dilutions. All tubes were incubated at room temperature for 18 hours and read for visible growth. End points were clear cut, and the sensitivity of the test organism under these conditions was consistently 0.016 micrograms of aureomycin per m.l. The method used for the in vitro experiments was as follows. To 5 m.l. quantities of a solution of aureomycin containing 800 micrograms per m.l., 0.5 m.l. of either amphojel, carmethose, or sterile distilled water, were added. After mixing, the tubes were placed in the incubator at 37°C. for 5 hours, at the end of which period they were kept refrigerated at 4°C. until they were assayed later on the same day. A 5 hour period of incubation was chosen because it is at this time that the maximum blood level has been found to occur following a single dose of aureomycin (8). Before assaying, the tubes were centrifuged at 2400 r.p.m. for 15 minutes. In the tubes containing aureomycin and water or aureomycin and carmethose, there was no sediment, and the fluid was homogeneously yellow. On the other hand, in the tubes with amphojel plus aureomycin, there was a large amount of yellow colored sediment, and the supernatant fluid was colorless. Samples for assay were prepared from the supernatant fluid of the amphojel-aureomycin tube, as well as from the resuspended sediment made up to the original volume with sterile distilled water. Assay methods were the same as described above for the in vivo tests.

RESULTS

As can be seen in Table I, 30 m.l. of liquid carmethose administered 15 minutes before a dose of either 750 mgm or of 1000 mgm of aureomycin had no significant effect on the assayable blood levels of this antibiotic. 30 m.l. of aluminum hydroxide gel, on the other hand, markedly lowered the blood aureomycin level in every instance. This is demonstrated graphically in Fig I.

In 2 additional subjects, 500 mgs of aureomycin were administered every 6 hours. Following a control period of 48 hours on this regime, 30 m.l. of carmethose was administered with each succeeding dose of aureomycin for 48 and 72 hours, respectively. No significant change in aureomycin serum levels was observed.

Figure 1



The in vitro experiments are summarized in Table II. They show a marked reduction of roughly 90% of active aureomycin in the control tubes. This is probably due to the instability of aureomycin at incubator temperature. The reduction was almost 100% in the tubes with aureomycin-amphojel, while the reduction in the control tubes and in the tubes with carmethose-aureomycin were of equal magnitude.

From the Department of Gastro-Intestinal Research and from the Department of Bacteriology and Virology, Medical Research Institute of Michael Reese Hospital, Chicago, Illinois.

*Aided by the Nelson Morris Fund. The Departments are in part supported by the Michael Reese Research Foundation.

**We are obliged to Drs. D. Radner and S. P. Bralow for some of the data.

***Kindly supplied by Dr. Stanton M. Hardy, of the Lederle Laboratories, Division of the American Cyanamid Co.

*Kindly supplied by Ciba Pharmaceutical Products Co.

TABLE I

SERUM AUREOMYCIN LEVELS 5-6 HOURS AFTER A SINGLE DOSE OF AUREOMYCIN IN GAMMAS PER M. L.

Subject No.	CONTROL # 1 750 mgm aureomycin	CONTROL # 2 750 mgm aureomycin	AMPHOJEL (30 ml) 750 mgm aureomycin	CARMETHOSE (30 ml) 750 mgm aureomycin
1.	2.5	2.5	0.3125	2.5
2.	4.0	4.0	0.01625	5.0
3.	2.0	2.0	0.325	2.0
4.	2.5	2.0	1.0	2.0
5.	5.0	4.0	0.625	4.0
6.	2.0	2.0	0.25	2.0
7.	4.28	1.25	1.25	4.0
	CONTROL # 1 1000 mgm aureomycin	CONTROL # 2 1000 mgm aureomycin	AMPHOJEL (30 ml) 1000 mgm aureomycin	CARMETHOSE (30 ml) 1000 mgm aureomycin
8.	5.0	4.0	0.625	4.0
9.	8.0	8.0	1.25	4.0*
10.	4.0	2.5	0.0625	4.0

*gastritis

TABLE II

IN VITRO ASSAYS OF TUBES CONTAINING 800 MICROGRAMS OF AUREOMYCIN EACH PER M. L.

	Incubation Temp. °C.	Added	Assay Titer
Control 1.	4	—	800
Control 2.	37 (5 hours)	—	80
Test 1.	37 "	Carmethose	80
Test 2.	37 "	Amphojel +	0.625
Test 3.	37 "	Amphojel + +	80

\+ Supernatant
++ Sediment resuspended to original volume with distilled water.

DISCUSSION

Our results with amphojel, confirming those of Di Gangi (7), Waisbren et al (4), Bartholomew and Nichols (6) and Seed and Wilson (3), demonstrate that aluminum hydroxide gel has a strong adsorptive action on aureomycin. It is obvious from the low serum aureomycin levels when the drug is given orally in combination with amphojel, that the adsorbed aureomycin is held fast in both, the acid pH of the stomach, and in the alkaline medium of the intestine.

The difference in adsorption of the antibiotic when administered with amphojel and carmethose can be explained by the differences in action of the two antacids. Amphojel is primarily a strong adsorbing agent, combining with gastric acid and carrying it out of the stomach, a small amount of it reacting chemically with the hydrochloric acid to form aluminum chloride. Carmethose, on the other hand, is an ion exchange buffer, combining with the hydrochloric acid in the stomach, and then releasing it in the intestine. It is also a good coating agent, adhering effectively to the mucosa of the stomach and small intestine (9,10). Recently, Bartholomew and Nichols (6) have used milk to overcome epigastric distress caused by aureomycin, and they have shown that blood levels of aureomycin were not affected. Probably the use of milk would be a simple and cheap method to use in aureomycin therapy when epigastric distress occurs. However, certain patients may need antacid and aureomycin therapy simultaneously, as in peptic ulcer, gastritis, etc. It appears now, that in such cases, antacids, particularly the adsorbents (3), should be tested to determine whether or not they affect serum levels of aureomycin before being administered with this antibiotic.

The in vitro experiments demonstrate that aureomycin is adsorbed by amphojel, but that it is not inactivated or destroyed by this process. However, it is evident that aureomycin is adsorbed so strongly on amphojel that most of it is not available for absorption into the blood stream. Thus, for local intestinal effects of aureomycin, amphojel might be used concurrently with the antibiotic. On the other hand, for effective systemic aureomycin

therapy, the simultaneous use of amphojel is contraindicated. No such effect was observed with carmethose, as evidenced by serum aureomycin levels comparable to the control values.

SUMMARY

30 ml of aluminum hydroxide gel, administered 15 minutes before a single oral dose of aureomycin, markedly depressed the serum aureomycin levels in 10 subjects. The simultaneous use of these two drugs is contraindicated. 30 ml of carmethose given in the same manner had no demonstrable effect on the aureomycin level of the serum, and effectively diminished the gastrointestinal disturbances frequently occurring with aureomycin therapy.

Amphojel adsorbs aureomycin in vitro. It does not destroy or inactivate the latter, but it seems to hold it firmly, not permitting intestinal absorption. Carmethose does not adsorb aureomycin in vitro, and does not interfere with intestinal absorption.

BIBLIOGRAPHY

1. Ross, S., Schoenbach, E. B., Burke, F. G., Bryer, M. S, Rice, E. C. and Washington, J. A.: J. A. M. A., 138:1213-1216, 1948. Aureomycin therapy of Rocky Mountain spotted fever.
2. Schoenbach, E. B. and Bryer, M. S.: J. A. M. A., 139:275-280, 1949. Treatment of primary atypical pneumonia with aureomycin.
3. Seed, J. C. and Wilson, C. E.: Bull. Johns Hopkins Hosp., 86: 415-418, 1950. The effect of aluminum hydroxide on serum aureomycin concentrations after simultaneous oral administration.
4. Waisbren, B. A. and Hueckel, J. S.: Proc. Soc. Exp. Biol. & Med., 73:73-74, 1950. Reduced absorption of aureomycin caused by aluminum hydroxide gel (Amphojel).
5. Boger, W. P., Matteucci, W. V., Beatty, J. O. and Baganz, H. M.: J. Phila. Gen. Hosp. 1:3-7, 1950 Aureomycin plasma concentration influenced by aluminum hydroxide.
6. Bartholomew, L. G. and Nichols, D. R.: Proc. Mayo Clin., 25: 370-373, 1950. Use of milk to control vomiting caused by aureomycin.
7. Di Gangi, F. E. and Rogers, C. H.: J. Am. Pharm. Assoc., 38: 646-647, 1949. Adsorption studies of aureomycin hydrochloride on aluminum hydroxide gel.
8. Schneierson, S. S. and Tobarsky, B.: J. Bact., 57:483-487, 1949. A method for the determination of aureomycin in the blood.
9. Brick, I. B.: Am. J. Digest. Dis., 16:315-319, 1949. Experiences with sodium carboxymethylcellulose as an antacid.
10. Necheles, H., Kroll, H., Bralow, S. P., and Spellberg, M. A.: Am. J. Dig. Dis., Jan. 1951. Peptic ulcer in man, Part IV. A new antacid made to meet requirements of antacid therapy. Chemical and laboratory work.
Bralow, S. P., Spellberg, M. A., Kroll, H., and Necheles, H.: A J. Dig. Dis., Jan 1951. Peptic ulcer in man. Part V. A new antacid, SCMC, made to meet requirements of antacid therapy. Clinical evaluation.

ABSTRACTS ON NUTRITION

KREHL, W. A. AND COWGILL, G. R.: *Vitamin content of citrus products.* (Food Research, 15, 3, 1950, 179-191).

Samples of fresh and processed citrus juices, as nearly homogeneous as possible, were withdrawn from a pooled composite sample representing a large number of boxes of citrus fruit in 17 Florida citrus processing plants. These samples were assayed for their content of ascorbic acid, biotin, folic acid, pyridoxine and inositol. Total solids and total acid also were determined. Biotin, folic acid and pyridoxine were present only in limited amounts in terms of practical nutritional significance. Ascorbic acid, as might be expected, was present in significant amounts and, in addition, the large amount of inositol present in the citrus products makes them a rich natural source of this vitamin.

WILLIAMS, R. J.: *Concept of genetotrophic disease.* (Nutrition Reviews, Sept. 1950, 8, 9, 257-260).

A genetotrophic disease is one which occurs if a diet fails to provide a sufficient supply of one or more nutrients required at high levels because of the characteristic pattern of the individual concerned. A partial genetic block involves a heritable trait characterized by diminution, but not complete failure, of ability to carry out a specific enzymatic transformation, thus increasing the need of the body for a specific nutritional factor or factors. Experimental animals if well fed will not become alcoholic addicts, because the urge on the part of animals to consume alcohol is conditioned by the existence of nutritional deficiencies. The concept may be applied to many diseases. When there exists a partial genetic block, i.e., failure of a metabolic process, the treatment might consist in supplying the products of the blocked reaction, but a more reasonable procedure is to increase the nutritional precursors to a concentration which would ensure necessary amounts of the metabolites, despite an inefficient reaction. The understanding of the rationale of this massive-type therapy is essential to the progress which the author believes is imminent.

KALISKI, S. R. AND MITCHELL, D. D.: *Treatment of diarrhea with Carob flour.* (Texas State J. M., 46, 9, Sept. 1950, 675-678).

Carob flour, marketed as "Arobon," is derived from the fruit of the Carob tree, and has been eaten as food since ancient times by the poor classes in some of the countries bordering the Mediterranean. 96 patients, most of whom were less than 1 year of age, suffering from both enteral and parenteral diarrhea were given Carob flour feedings, and results graded with reference to the number of hours required for improvement in the frequency and consistency of the stools. Good results,—stool improvement in 48 hours—were obtained in 64 cases, fair in 13, and poor in 19. The average hospital stay was only 9.9 days. The authors believe Carob flour is a useful adjunct in treating diarrhea in young children, but as Dr. B. A. Knickerbocker, in discussing the paper, pointed out, the cases were so skilfully managed in all other respects, that it is questionable how much the excellent results depended on the use of Carob flour, which contains 50 percent carbohydrate and only 4 percent protein.

DAUM, K., TUTTLE, W. W., MARTIN, C. AND MYERS, L.: *Effect of various types of breakfasts on physiological response.* (J. Am. Diet. Assn., 26, 7, July 1950, 503-509).

Physiologic response is judged partially by measurements of tremor magnitude, and partly by choice reaction time. Neither of these phenomena were affected in 10 women by either 1,000 cal. or 300 cal. breakfasts. As compared with no breakfast, one containing 600 calories showed definite improvement in both phenomena and an increase in maximum work output in 80 percent.

HYDE, J. S. AND RICHMOND, J. B.: *Vitamin D intoxication in a child with rheumatoid arthritis.* (Am. J. Dis. Child., 80, 3, Sept. 1950, 379-389).

The effects of large doses of vitamin D were observed in a 12 year old girl with rheumatoid arthritis. Daily doses of 100,000 to 150,000 U. S. P. units of a proprietary irradiated ergosterol product were given for five and one-half years. Toxic manifestations of renal insufficiency and metastatic calcification of soft tissues were absent. After discontinuance of vitamin D therapy, some amelioration of symptoms was noted but there was no improvement in renal function after 2 years' observation, indicating irreversible kidney damage.

EPSTEIN, I. S., MACKAY, M. A. AND TURNER, C. N.: *Control of malnutrition.* (Med. J. Australia, June 17, 1950, 799-802).

33 patients attending a Research Unit of the Royal Melbourne Hospital and who showed definite malnutrition were studied to determine how amenable the malnutrition might be to control. Among the leading causes of malnutrition were alcoholism, living alone, an occupation tending to skimpy and irregular meals, faulty "therapeutic" dieting, poor food habits, food fads and organic disease. Alcoholism was the cause in the largest number and proved the most difficult

factor to control. Poor food habits and fads were heavy contributors but proved to be more easily corrected by dietetic instruction. About one-third of all cases were controlled, one-third partially controlled and one-third uncontrolled. It appeared that, under stress, women neglect their meals more than men. The authors caution that therapeutic diets may easily lead to malnutrition unless carefully supervised and supplemented.

BLACK, R. H.: *Hepatomegaly in the natives of Northern Australia.* (Med. J. Australia, July 1, 1950, 10-12).

In the course of a survey in Northern Australia for the detection of malaria, none was found, but in examining 1382 natives, enlargement of the liver was encountered in 16.5 percent, chiefly among adults. It is proposed to make further examinations including liver biopsies on these cases, but in the meantime Black favors the idea that this hepatomegaly develops on a nutrition basis. The diet of the natives is deficient in fresh fruit and vegetables, and part of the time the natives live a nomadic existence with uncertain food supplies. Possibly these natives have fatty livers, as in Kwashiorkor. No jaundice or ascites was found.

HAMMER, J. M.: *The role of vitamin therapy in chronic ulcerative colitis: a case report.* (Harper Hosp. Bull., 8, 4, 114-120).

In the case of a 22 year old female suffering from chronic ulcerative colitis, associated with paranoid and hostile tendencies, the injection intravenously of 10 c.c. of Sol-U-B produced a dramatically favorable change overnight in her physical and mental condition, and from this point she progressed, with obvious arrest of the disease, although previously she had made no progress on dietetic, antibiotic and chemotherapeutic treatment. The results raise the question as to *why* "flooding" the enzyme systems with vitamin B complex produced so miraculous a change. The author reviews much literature to indicate that diarrhea may result from vitamin deficiencies, and that vitamin B Complex deficiency can easily and quickly result from a high carbohydrate and low protein diet. Infection may indeed be but a secondary factor. Although the report concerns but a single case, the principle of "flooding" with B Complex vitamins should be given a wider trial.

FULD, H.: *Effect of vitamin B_{12} on neuropathy in pernicious anemia treated with folic acid.* (Brit. Med. J., July 15, 1950, 147-148).

The case of an old lady of 74 is reported who had been placed on folic acid therapy for pernicious anemia, because of skin sensitivity to liver extract. After 15 months she developed subacute combined degeneration of the spinal cord and a delusional psychosis although the blood levels were not low (hemoglobin 78 percent and R. B. C. 3,500,000). She received 40 micrograms of vitamin B_{12} followed by 20 micrograms every third day for two weeks, every fifth day for two weeks and every 7th day for 6 weeks. The total injected vitamin B_{12} was 0.5 mg. She made very rapid recovery, the psychosis disappearing in 5 or 6 weeks, and with arrest of the spinal cord changes. The blood levels reached normality after four weeks. The case illustrates the danger of relying upon folic acid in the treatment of P. A. and also the dramatic improvement on vitamin B_{12}.

TROWELL, H. C.: *Problems raised by Kwashiorkor.* (Nutrition Reviews, 8, 6, 161-163).

Kwashiorkor is a disease affecting millions of African infants of 2 to 3 years of age, characterized by great mental irritability; puffy features, slight or severe generalized edema; brown, soft, scanty hair; an abnormally pale skin; bulky, loose stools containing a fair amount of all varieties of undigested food; slight anemia and a protracted course. The disease almost invariably is associated with some form of infection, which may vary from malaria or hookworm to pneumonia. A fatty liver usually is present. The pancreas shows atrophy of the acinar cells. The gastrointestinal tube is thinned and atrophic. The serum albumin invariably is reduced. A fine cirrhosis occurs in the portal tracts of the liver and periphery of the hepatic lobule, following the disease, and may possibly explain the high incidence of liver cirrhosis in African adults. The glands of internal secretion are affected. The opinion has been held for some time that the dominant defect in Kwashiorkor is that of protein inadequacy. Investigations of the metabolism are being undertaken now in Uganda.

UCKO, H.: *Dietary treatment of hypertension.* (Brit. Med. J., July 15, 1950, 144-147).

Kempner's rice diet, a barley diet, and a low sodium diet were tested on 14 unselected cases of hypertension—3 men and 11 women. Three of the patients had chronic renal disease, one was diabetic, and the youngest female was an instance of Cushing's syndrome. All others suffered from essential hypertension. Some fall in blood pressure occurred in all patients but the extent varied. The low sodium content of the diets was regarded as chiefly responsible for the effect. The patients all *felt* better.. It is not justifiable to keep a patient on a low sodium diet very long unless he happens to be one who greatly benefits from the standpoint of hypertension, because of social inconvenience. The theoretical implications of this work are important in that they support Selye's theory of the diseases of adaptation. On a low sodium intake the adrenals appear to be unable to produce the abnormal mineralo-corticosteroids which are regarded as responsible for vascular disease.

EDITORIAL

SOCIAL TRAUMATISM AND ULCER

Every dogma advanced to explain the pathogenesis of peptic ulceration admits of exceptions. The constitutionality of ulcer people favors the long, thin, dynamic individual, but this disease also occurs in fat men who give no evidence of being hyperkinetic. Perfectionism, and craving for superiority and affection, are not unusual human characteristics, certainly not the proprietary mark of peptic ulcer. Achlorhydria prohibits the formation of ulcer and thus saves 25 percent of the adult population from ever having ulcer, although many of these people are long, lean, dynamic and restless. Physical and mental characters undoubtedly may favor or prevent ulcer development, but the environment also may work both ways. The individual's own reaction to his particular life-situation is the crucial factor.

A study of individual reactions makes it clearer that anxiety and uncertainty, often mixed with fear, provide a psychic state favoring ulcer in those whose constitutions permit the disease. The experience of the British Army in W. W. II revealed the surprising fact that the vast majority of duodenal ulcers found among soldiers had begun in civil life prior to entering the service. This finding suggests that, disturbing as armed combat may be, it possesses a modicum of grim certainty, which unfortunately cannot be said of civilian existence.

Both Western and Eastern civilizations today are so loaded with causes for anxiety, uncertainty and tension that those persons capable of ulcer development will, more regularly than ever, actually acquire the disease. The various human constitutional types, with their multiplex reaction patterns, do not change even from century to century, but the social influences affecting

men and women have undergone drastic and unbelievable changes during the past seventy years. The industrial revolution, the unending strife between labor and capital, the baffling complexity of our present economic organization, the transformation of governmental activities into stereotyped bureaucracy, the impact of science upon technology and human thought, and the moral collapse of society as reflected in the divorce rates and in the abrogation of contracts from lowest to highest levels are only a few of the disturbing developments which preceded the present world-wide ideological and racial conflicts. These and other factors have altered, beyond recognition, our previous philosophic and instinctive estimates of the world we inhabit.

The impingement of this altered society upon the individual in terms of livelihood, aspiration and emotional security is well-known. Uncertainty which always characterized human experience was never previously so uniform and unrelieved. We must regard our civilization partly as a *traumatic* society, whose injuries to man are not confined to the battlefields, the wreck-strewn highway nor the pocketbook. The chief trauma of all is inflicted upon the Ego, conceived in love and dedicated to the controversial proposition that life is wonderful, and the world as gentle as a fairy tale. That Ego is everyman, particularly he who fails to discover any objective confirmation of his infantile optimism, but realistically faces the fact that he is moving in a somewhat dangerous social current.

The traumatic element in the individual's reaction to our present civilization is a pervading uncertainty which induces a state of chronic anxiety. If he be a person with acid gastric secretion, a worshipper of perfection and success, and particularly if he has not lost his infantile demand for security and affection, he may, under some intensification of environmental stress, express himself most fluently by developing a small, round, red ulcer in his duodenum.

While the human environment unfortunately cannot be altered at will and made less traumatic for the sake of those persons whose reactions lead to peptic ulcer, hypertension or hyperthyroidism, there is always the possibility that the individual's attitude toward his environment may change, thus decreasing the likelihood of disease. This is one of the most difficult phases in the treatment of ulcer, but it must be increasingly employed by the physician. That it involves a very fundamental alteration in the personality seems undeniable, yet sometimes it may be brought about without technical psychiatry.

A wealthy executive with a large and ancient duodenal ulcer, on completion of his diagnosis, raised the most strenuous objections to a time-table of powders and milk, diets and the deprivation of tobacco and alcohol. He was told he might indulge without limit in tobacco and whisky, and eat the most harmful kinds of food, *provided* that he would go alone to the Ozark Mountains, leaving his wife and his business behind, and live for a whole year in a cabin, cooking his own meals, cutting his own wood and refusing all interruption from his office staff. For some reason, he accepted the challenge of this unusual suggestion, faithfully carried it out and returned a year later, rejuvenated and without an ulcer. During the dozen years elapsing since his Ozark hibernation, there has been no recurrence of ulcer. He still smokes and drinks and overworks, but he appears to have forever lost his anxiety. In the cool mornings in the mountains when the placid lakes reflected the imagery of the forests and in the evenings when the clear sky was filled with stars, a man learned the one lesson he needed—that the struggles of civilization, valuable as they are, are not valuable enough to consume one's whole being. He now plays the game of life with gusto, but also with detachment. Some kind of acquired indifference undoubtedly cured his ulcer.

Not infrequently the lesson of detachment can be taught without resort to so unusual a form of therapy. Many persons, upon being told that their ulcers are merely visible expressions of anxiety, make a rapid calculation of values, with peace of mind coming out on top.

FREE DIETING "DOWN UNDER"

The English-speaking medical world (with some exceptions) believes that strict dietary control of diabetics is an indispensable feature in the treatment of this wide-spread disease. Every few months, however, someone advocates "free-dieting" and presents data which *appear* to support his contentions. At the recent Brisbane meeting of the Australian Medical Congress, the subject was again brought up and, as usual, considerable polemics developed. Bruce Hunt, M. D., read a paper entitled "Why Diet the Diabetic?" in which he analyzed the records of a series of 191 diabetic patients in his private practice between 1946 and 1950. All patients, except 19, received adequate doses of protamine zinc insulin. He advises dieting only to overcome adiposity. Otherwise his only "don't" was directed against eating much sugar or cake late in the afternoon. He had not found arteriosclerosis developing because of free-dieting but rather from the inadequate use of insulin. In the discussion, J. Cobley pointed out that the control of hyperglycemia was the object of treatment, hence the use of restricted diets was important. S. Robertson spoke on behalf of Hunt's contentions and said that the use of free diet for children since 1932 in one of the important Scandinavian clinics had not resulted in a greater incidence of vascular disease than that shown by the figures of Priscilla White. Dr. Lancaster said that Joslin's statistics in diabetes were an example to the rest of the world. Dr. T. E. Lowe thought that the speakers on both sides had been guilty of dealing entirely with a problem of practical politics and he supported a plea for a thorough scientific investigation of the problem. There were two opposing groups conducting a large-scale experiment in human physiology, and it behooved everyone to discover on which side lay the proof.

As of now, in America, it would appear that the use of diabetic diets has won against the "free-dieters." It is very difficult indeed to disregard the scientific findings of Joslin, Root, John and many others, or resist the impression that strict control is of the essence of sound diabetic management.

BOOK REVIEWS

PARS PRO TOTO. Alfred Peyser, 200 pages, Almqvist and Wiksell, Stockholm, 1950.

An international key to medical abbreviations, including sister sciences in six languages was long overdue, and the present concise volume, containing an unbelievable number of abbreviations with their interpretations, will be most welcome to those who have been vexed, year after year, by encountering letter-signs which could have no possible meaning. For example, "a lecture on PABA given by Mr. Brown, M. D., D. P. M., M. E. F. at a meeting of Ufaw" *means* A lecture on paramino-benzoic acid given by Mr. Brown, M. D., Diploma in Psychological Medicine, Middle East Forces, at a meeting of Universities Federation for Animal Welfare. Mr. Peyser must have been prodded into this tangled research by personal exasperation, and he has put us all in his debt. From now on, no one can safely flaunt N. S. A. G. B. before our eyes for we know it means Nursery School Association of Great Britain and VESKA Will no longer conceal Verband Schweizerischer Krankenanstalten. Everyone should buy this little volume in the name of mental hygiene, as an antidote to hypertension, in an age too busy to spell out a single word when it can be symbolized by a single letter.

LA DIABÈTE SUCRÉ. Raoul Boulin, 2nd Edition, 121 pages. L'Expansion Scientifique Francais, Paris, 1950.

A number of separate essays are embodied in this brochure, the longest being devoted to bronzed diabetes. Other subjects dealt with are the blood sugar in the diagnosis of diabetes, hypoglycemia and pancreatic traumatism, the sequellae of hypoglycemic accidents, and globin-zinc insulin. French thinking and practice in diabetes follows closely our American attitudes. The volume will prove valuable to all practicing physicians.

GENERAL ABSTRACTS OF CURRENT LITERATURE

RICKMAN, J. H.: *Duodenal diverticula: their incidence and clinical importance.* (Alex. Blain Hosp. Bull., 9, 1, 3-8).

The majority of duodenal diverticulae produce symptoms, the commonest of which is epigastric discomfort. Medical treatment is unreliable and two cases are reported in which symptoms were relieved by removal of the diverticulae. It is suggested that surgery might more frequently be employed.

NEWTON, M.: *Acute diverticulitis of the cecum.* (Amer. Pract. and Digest of Treatment, 1, 3, 277-278).

The author reports 8 cases of diverticulitis of the cecum which were seen at the Hospital of the University of Pennsylvania over a ten year period. To distinguish this disease clinically from acute appendicitis is difficult, and even with the abdomen opened, the presence of a hard inflammatory mass may present diagnostic difficulties. Whenever possible, simple excision of the inflamed diverticulum is the treatment of choice.

MARKOFF, N. *Ueber die chronische Form der epidemischen Hepatitis (Chronic epidemic hepatitis).* Schweiz. med. Wschr.; 4 Febr. 1950; vol. 80, No. 5; 93-98.

The frequency of epidemic hepatitis amounted to 16.6 (1943) and 9.6 (1944) per 10,000 inhabitants of Switzerland; 5 to 18% of these cases become chronic, i.e. an hepatic injury still remains after 3 to 4 months. It must be distinguished from the general long lasting digestive sequelae of jaundice; with neuro-vegetative phenomena, the gallbladder diseases and the "hepatogenic gastric ulcer."

The chronic hepatitis develops mostly with patients whose liver was previously defective; during climacteric years; or with insafficiently treated patients. Dietical mistakes, too early overwork, or secondary infection have the same effect. The acute stage may often stay inapparent when anicteric, and is diagnosed as "flu." Some cases of chronic hepatitis have a wavelike course, with subacute outbursts; others remain latent before appearing as a real cirrhosis.

The symptoms of chronic hepatitis are various: the patient is rapidly tired; he complains of indefinite gastro-intestinal signs, as lack of appetite, flatulence, diarrhea, intolerance to fats, pains in the liver, alternating with vasomotory symptoms such as dizziness, sudden perspiration, blushing, etc. The temperature rises slightly, the liver and spleen are *a little* enlarged, spider telangiectasis appear on the skin.

The treatment is the same as for liver cirrhosis, rest being the most necessary.

M. DEMOLE, Geneva.

KUNKEL, H. G. AND LABBY, D. H.: *Chronic liver disease following infectious hepatitis, II. Cirrhosis of the liver.* Ann. Int. Med., 32, 3, 433-450.

The authors report 5 cases in detail, in each of whom severe hepatic cirrhosis followed an attack of infectious hepatitis. Characteristic of these cases were severe abnormalities in the various serum proteins and, late in the disease, marked hepatic and splenic enlargement, causing the syndromes to resemble what in the past was known as Banti's disease. The disease differed from Laennec's cirrhosis in that it was progressive and not much affected by treatment. The characteristic pathological lesion was an irregular nodular hyperplasia of liver cells between broad areas of contracted reticulum and fibrous tissues. In search for contributing factors in the development of this disease, the authors felt that strenuous activity during the initial attack and luring relapse was of importance. Alcohol seemed to play a part. Finally, it was the older individuals and not the younger ones who went on to cirrhosis.

BROWN M. BRESNAHAN, T. J., CHALKE, F. C. R.; PETERS, B., POSER, E. G. AND TOUGAS, R. V.: *Personality factors in duodenal ulcer.* Psychosomatic Med., 12, 1, 1-5.

As a result of Rorschach tests on 25 duodenal ulcer patients, with suitable controls, evidence was found of the ulcer patients' conflict between an overly active disposition on the one hand and passive needs on the other. In simpler language, ulcer patients, as a group, tend to deal with their environment at an impulsive, emotionally immature level, leading to a conflict in the area of social interpersonal relationships.

AKERLUND, AKE AND RUDHE, ULF. *Intramural small cystic diverticulosis of the gallbladder.* Acta Rad. 33, 2, 147. Febr. 1950.

An account is given of a new roentgen finding typical of intramural diverticulosis of the gallbladder. This is based on the authors' observations in conjunction with two cases from the literature. The findings consist of a more or less continuous narrow streak of contrast, immediately adjacent to the shadow of the gallbladder and following it for varying distances. This contrast (corona) shows in places a suggestion of granulation or columnar structure. The radiological picture is due to the composite effect of contrast filling of a large number of closely packed intramural diverticula. The importance of diverticulosis of the gallbladder in the origin of the aseptic, cholesterol concretions of radiate structure in the retention gallbladder is stressed.

FRANZ J. LUST.

KLEINERMAN, J., YARDUMIAN, K. AND TAMAKI, H. T.: *Primary carcinoma of duodenum.* Ann. Int. Med., 32, 3, 451-465.

Primary carcinoma of the duodenum is extremely rare. It was found in only .035 per cent of approximately one-half million autopsies. The authors present two cases of primary cancer of the suprapapillary of the duodenum, both of

whom died. The diagnosis of primary carcinoma of the duodenum is probably one of the most difficult problems confronted in medicine. One reason is a lack of characteristic signs and another is that we usually do not consider its possibility. Nevertheless, Dixon at the Mayo Clinic made correct pre-operative diagnoses in 35 out of a series of 37. Radiologically the lesion may be mistaken for duodenal diverticulum. Gross hemorrhage is a notable feature and a cause of death.

COOK, J. E.: *A plan for avoiding sensitization reactions to liver injections.* Ann. Int. Med., 32, 3, 506-509.

Briefly, Cook found that allergic reactions to parenteral liver extract could be prevented by spacing the doses 2 days instead of 2 weeks apart. First, the sensitive patient must be gradually desensitized by giving frequent, highly diluted doses and once desensitization is accomplished, then a small dose every 48 hours is given, the patient being taught how to administer the preparation himself, similarly to insulin in diabetes. Cook makes a statement which is contrary to accepted doctrine (but with which the abstractor is in agreement), that the patient is sensitive to *liver extract* not specific animal protein, so that using a different animal source does not usually meet with success. The author describes 2 cases of sensitivity in which Reticulogen was successfully used by his method. He does not mention having found any cases allergic to pure vitamin B_{12} or B_{12b}.

HAUDENSCHILD, W. *La proctalgie fugace: Fugitive proctodynia.* Rev. Med. Suisse rom.; June 1950; vol. 70; 349-355.

This symptom complex, described by McLennan in 1917, is made up of acute pains, which the patient feels on the side of the rectum, an inch or two above the anus. These appear irregularly, usually after a long interval (often a year), in the middle of the night. The proctodynia may be so acute that the patient faints; it disappears by itself in 5 minutes to 2 hours, but every patient has found his own remedy to shorten the attack: hot compresses, hip-bath, warm enema, etc. After each attack the patient feels very tired and needs a long sleep.

H. reviews the literature and discusses the differential diagnosis with the rectal pains of patients suffering from tabes, with ordinary proctalgia or coccygodynia. The etiology is still unknown; the familiar type is frequent. From the clinical appearance of this disease, H. thinks it looks like erythromelgia, and believes it comes from a vasomotory disorder: intermittent ischemia of the levator ani muscle. In some cases it seems to have a traumatic or allergic origin.

Apart from sedatives, the treatment is chiefly local with physical means.

M. DEMOLE, Geneva.

WAGGONER, C. M. AND LEMONE, D. V.: *Clinical and roentgen aspects of internal biliary fistulas.* Radiol., July 1949, Vol. 53, No. 1, 31-41.

In a review of the literature prior to 1941, only 90 cases of internal biliary fistula diagnosed by x-ray were found. The authors add 13 additional cases. The clinical findings were inconsistent. Only cases due to new growth presented palpable masses. Scout films of the abdomen revealed abnormal air patterns in all cases involving the gall-bladder (70 per cent). In cholecystocolic fistula the air patterns were final for diagnosis, but not so in fistulas between the gall-bladder and duodenum, and such patterns were not present at all in choledochal fistulas or those associated with cancer. All fistulas, however, were easily demonstrated by barium studies of the G. I. tract except where blockage was present due to cancer or perforating stone.

SENGPIEL, C. W.: *The compatibility of castor oil and Priodax in concurrent examinations of the colon and gallbladder.* Radiol., July 1949, Vol. 53, No. 1, 75-79.

The author found that giving castor oil prior to the ingestion of Priodax did not interfere with satisfactory visualization of the gallbladder. For that reason the gall bladder and colon may be examined concurrently at one appointment.

FLEISCHNER, FELIX G. AND BERNSTEIN, CHARLES.: *Roentgen-anatomical studies of the ileo-cecal valve.* Radiology 54 43. January 1950.

A comparative roentgen-anatomical study of the ileocecal valve has been undertaken on the basis of 50 normal postmortem specimens and selected roentgenograms from approximately 200 clinical examinations. Many variations in the morphology of this region have been encountered and described. Distinct types could be observed, the prevailing pattern of which presented the following roentgenologic appearance: the terminal ileum rising from the pelvis in a reverse S-shape is implanted into the medial colonic wall, projecting into the lumen for 2 cm. This intracolonic area, representing the valve itself, is flattened so that it forms a wedgeshaped lumen, opening through a horizontal slit into the colon. The upper and lower walls of this flattened area are the upper and lower lips of the valve, seen as bandlike negative shadows, 3-5 mm. in width converging towards the center of the colon. The barium filled area between the lips varies from an elongated evenly calibered channel to a short, plump cone. The upper lip is longer than the lower lip and fuses with the posterior shelf (frenulum) so that the filling defect caused by the upper lip extends almost to, or even as far as, the lateral wall of the colon. All these details are best observed by application of pressure. When the ileum is implanted into the posterior of the colon, the valve presents itself headon in the postero-anterior view. With pressure applied, a plump spindle shaped negative shadow is seen, often extending across the entire width of the colon or sometimes even centered more laterally. A linear barium density in the axis of the spindle represents the opening of the valve.

The lateral wall of the terminal ileum and the medial wall of the cecum may be fused over a fairly long distance. If the spacing between ileum and cecum is even in width, with both contours smooth and parallel, this is considered a normal variation rather than the result of inflammatory adhesions. An excessive accumulation of fatty tissue in the lips of the valve, or protrusion of ileal mucosa beyond the lips of the valve, may cause a rounded tumor-like filling defect in the colon. Recognition of these instances as normal variations rests upon the intimate relationship of the mass to the valve; the smooth rounded contour; the lack of obstruction, local tenderness, or other signs of abnormality in the ileocecum; and the change in size or shape (with herniated mucosa). However, this distinction is not always possible, and in such instances the final decision rests on clinical evidence. Insertion of the terminal ileum into the lateral wall is considered not to be within the normal range of variation. Persistently visible Kerckring's folds in the terminal ileum occur with disease in the ileocecal region and their presence should arouse suspicion of the presence of associated lesion.

FRANZ J. LUST.

SCHWARTZ, R.: *A modified test for stool trypsin.* Arch. Ped., 67, 4, 165-169.

Schwartz has produced a convenient modification of the Schwachman-Patterson-Laguna x-ray film test for trypsin in the stool. Schwartz suspends a strip of exposed but undeveloped film in a diluted stool mixture in a Wassermann tube, corks it up and permits it to incubate in the vest pocket for 30 minutes. In two cases of fibrocystic disease of the pancreas the test was positive (no trypic activity) while 60 control tests were negative (definite trypic activity). This test should constitute a simple, inexpensive method of screening patients, before going to the more elaborate methods of duodenal intubation and vitamin A plasma determinations.

LEVENE, G. AND BRAGG, E. A.: *Mobility of the rectosigmoid.* Radiology, 54, 5, 717-725.

Lateral roentgenograms taken before and after evacuation of a barium enema are valuable in detecting fixation of the rectosigmoid in various types of pelvic disease. Normally, the distended gut lies close to the hollow of the sacrum, and after evacuation the upper rectal ampulla and sigmoid fall away from the spine. Failure of these segments to move is usually an indication of disease in the pelvis, arising either within or outside the gut.

SAEGESSER, F.: *La résection d'estomac pour exclusion des ulcères gastroduodénaux inextirpables. Gastrectomy excluding peptic ulcers which cannot be removed.* Rev. Méd. Suisse rom.; August 1950; vol. 70; 473-485.

Gastrectomy is, nowadays, the best surgical treatment of the peptic ulcer, which in this way is safely cured.

But it is not always possible to remove the ulcer with the stomach, when it is located near the cardiac orifice, or far away on the duodenum. Madlener suggested in 1923 to make a broad gastrectomy, *leaving the ulcer*. S. has controlled the operated patients of the Surgical Clinic, Lausanne, and declares that, after a long while, they are still in very good condition, if a few technical cares are taken.

The only danger is the bleeding of the remaining ulcer, but it happens rarely and only as an immediate consequence of the operation. S. has never seen a late hemorrhage or perforation.

The "gastrectomy excluding the ulcer" is a useful method: when using it, one avoids mutilating operations such as total gastrectomy; insufficient ones such as gastroenterostomy or vagotomy; or dangerous ones as in some duodenal ulcers located too far. Thanks to this technic, the mortality, after gastric operations, is kept very low, without diminishing the percentage of good results. This has a great importance: if the surgeon wants to remove completely the morbid part of the stomach, the patient often runs an unnecessary risk and the concientious surgeon will hesitate to operate in this case. Now the gastric resection conducted this way, says S., is less dangerous than keeping an ulcer that might bleed, or perforate or develop into cancer!

M. DEMOLE, Geneva.

WILLIAMS, R. B.: *Summary of salmonella and shigella of Alaska.* Northwest Med., 49, 5, 340-41.

During the past 15 years there have been many cases of gastroenteric disease, associated with high fever, marked diarrhea and dysentery occurring in all parts of Alaska. Many of these cases are of the bacillary type with quick cholera-like dehydration and with blood and mucus in the stools. Difficulty has been experienced in obtaining stool specimens for bacteriological examinations owing to transportation difficulties and distances, but between 1944 and 1949 a total of 1082 stool, urine and blood specimens were examined. Of this number it was possible in 118 instances to isolate Gram-negative bacteria of the general *Salmonella* and *Shigella* of the family *Enterobacteriaceae*. Vaccination programs have been carried on by the health agencies in Alaska, but sanitation offers the best long-term preventive measure against typhoid. An investigation now is in progress to determine the sanitary measures necessary. The role of permafrost (permanently frozen underlying ground) in the transmission of these diseases is not clearly known.

FERSHING, J. AND BAKER, L. A.: *Salt excretion in liver disease.* Illinois M. J. 97, 5, 251-258.

Salt restriction has a place in treating decompensated cirrhosis of the liver, since the authors found that, in many such cases, the excretion of a single large dose of sodium chloride (20 gm.) was greatly delayed. In other cases there tends to be less salt retention, so that restriction of sodium chloride may be advisable only for short periods of time. The degree of salt retention apears to be more closely associated with the degree of portal hypertension present, than with any other known factor. For that reason, the salt tolerance test may be a useful method of estimating portal hypertension. Cases of acute hepatitis do not show salt retention, and there is no need to restrict salt in the diet.

GLASS, G. B. J.: *Defective thermal coagulation of blood serum in cancer and other diseases and its clinical interpretation.* Journal Mount Sinai Hospital, 17, 1, 1.

The incidence of defective thermal coagulation of serum in disease differs from that of most of other nonspecific serological tests. This is due to its different mechanism and dependence upon quantitative and probably also qualitative changes in the serum albumins. For this reason it gives information which cannot be obtained by testing the sedimentation rate, protein content of the serum, or various flocculation reactions based upon disturbances in gamma-globulins of serum. Herein lies the main value of the test of defective thermal coagulation of serum, and because of this it may prove very useful as a diagnostic and prognostic aid within the frame of the entire clinical picture and in association with other laboratory data.

The thermal coagulation defect of serum may be detected by the simple technic of determination of the thermal coagulation point of serum (TCPS) much easier than by measurement of the iodoacetate index with Huggins technic, and the information obtained is similar in significance.

The thermal coagulation point of blood serum follows to a great extent the course of disease and serves as an index of the severity of the underlying pathological process.

The defective thermal coagulation of blood serum, whatever its ultimate value, is not the principle upon which a reliable cancer test can be based. It has only a limited diagnostic value in some selected groups of malignancy, but it definitely does not belong to the cancer clinic and it cannot be applied to general cancer diagnosis and to screening of early cancer cases among the population because of the high incidence of false negative and false positive results.

The test based upon the principle of defective thermal coagulation should therefore not be called by the misleading name "blood test for cancer." All available evidence indicates that defective thermal coagulation of blood serum, without regard of the method by which it is tested, is a very useful but entirely non-specific serological index of serious organic illness.

FRANZ J. LUST.

BLAIN, A. W. AND BLAIN, A., III: *Ligation of the splenic artery, the operation of choice in selected cases of portal hypertension and Banti's syndrome.* Alex. Blain Hosp. Bull., 9, 2, 130-137.

Ligation of the splenic artery, first studied experimentally and first performed for Banti's syndrome in 1913 by A. W. Blain, has never been a widely employed operation but deserves more frequent application. It is the operation of choice in case of "poor-risk" splenomegaly due to portal hypertension, Banti's syndrome and occasionally other forms of splenomegaly. In portal hypertension, if the patient's condition is poor, or if the surgeon is not familiar with the technique of spleno-renal anastomoses, ligation of the splenic artery is preferable to splenectomy. There is less interference with anastomotic venous pathways and subsequent spleno-renal anastomosis will be easier, should the patient's improvement permit the operation.

STEINMANN, B.: *Sympathektomie und ulcus pepticum (Sympathectomy and peptic ulcer)* Schweiz. med. Wschr.: 8. July 1950; vol. 80, No. 27; 695-697.

An operation on the vagus or on the sympathetic nerves ruins the balance between these antagonistic systems. Cutting out some neurovegetative elements, not only inhibits the system which has been removed, but produces, sometimes later, an exaggerated activity of the other system.

The medical literature gives numerous examples of arterial hypertension consecutive to vagotomy for peptic ulcer. Inversely, some peptic ulcers have been aggravated after thoraco-lumbar sympathectomy for hypertension.

The case reported here concerns an 18 year old girl, with hypertension of 210/110 mm. Hg., probably due to a renal anomaly, who was sucessfully treated by bilateral splanchnicectomy using Smithwick's method. The blood pressure was lowered and kept between 110 and 140 mm. Hg. maximum. Fifteen months later, very important digestive bleedings appeared and compelled the surgeon to an urgent gastrectomy: it showed a probably ancient duodenal ulcer, at that time in full development: an erosed artery was the reason for the bleeding.

The pathogenesis of these ulcerous complications after sympathectomy is dependent to following facts:

1) Lack of sensitiveness in the upper gastro-intestinal tract. The typical ulcerous pain rarely appears, and one must give attention, with these patients, to the slightest symptoms.

2) After sympathectomy the gastro-duodenal physiology is modified: the peristalsis is greatly increased.

3) Sympathectomy inhibits arterial vaso-constriction, facilitating any kind of bleeding.

These facts show the importance of neurogenic factors in the development of peptic ulcers; and requires a thorough digestive anamnesis before practicing a sympathectomy.

M. Demole, Geneva.

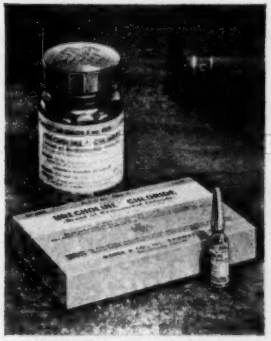
To Prevent or Control Postoperative Urinary Retention

Bladder Atony

Intestinal Atony

Urecholine® Chloride provides the much-desired answer to the distressing problem of urinary retention. It may be employed as an effective means of *prevention*, by routine administration following abdominal surgical procedures. Equally effective when used for *treatment*, Urecholine affords prompt relief and obviates, in a large percentage of cases, the necessity and inconvenience of catheterization. Reproducing the effects of parasympathetic stimulation, the drug is effective also in the treatment of *chronic* or functional urinary retention, when due to muscular atony without obstruction.

Urecholine Chloride has been found equally beneficial in the prevention and relief of postoperative abdominal distention, in gastric retention following vagotomy, and in selected cases of megacolon.



Supplied as 5 mg. tablets in bottles of 100 for oral use, and in cartons of six 1 cc. ampuls, 5 mg. per cc., for subcutaneous injection.

Literature concerning Urecholine Chloride is available upon request

COUNCIL ACCEPTED

MERCK & CO., Inc
Manufacturing Chemists
RAHWAY, NEW JERSEY

MERCK

Urecholine® Chloride

(Brand of Bethanechol Chloride)
(Urethane of β-Methylcholine Chloride Merck)

CANCO PROMOTES THREE TO SALES EXECUTIVE POSTS

E. K. Walsh has been appointed assistant general manager of sales for the American Can Company and B. R. Wood has been promoted to succeed him as manager of sales for the Atlantic division, it has been announced by L. W. Graaskamp, vice-president in charge of sales.

Mr. Wood, previously assistant manager of sales for the Atlantic division, is succeeded by G. F. Henschel, formerly a sales division manager in the Atlantic division, Mr. Graaskamp said.

Mr. Walsh began his career with the can company in 1929 in the firm's Hudson plant in Jersey City, N. J. A year later he was transferred to Atlantic division sales. In subsequent years he held a number of sales posts in New York, later serving as local sales and district sales manager in Baltimore. He was appointed assistant manager of sales for the Atlantic division in 1947 and early this year became manager of sales for the division.

Mr. Walsh was graduated from Dartmouth College in 1929. He served in the Navy during World War II with the Supply Corps and later as officer in charge of the Containers Section of the Bureau of Supplies and Accounts. He is a native of Washington, D. C., and now resides in Chappaqua, N. Y.

Mr. Wood began his career with Canco in the firm's Englewood plant in Chicago in 1926. The following year he was transferred to the Chicago general sales office, where he became a salesman and later sales representative for packers' can sales. In 1942, Mr. Wood was transferred to Indianapolis as a sales representative and two years later was appointed sales manager for the Indiana district sales department.

Mr. Wood went to New York in 1948 as sales division manager and in January of this year was named assistant manager of sales for the Atlantic division.

Mr. Wood was graduated from Miami University, Oxford, Ohio. He is a native of Baltimore and now resides in Ardsley-on-Hudson, N. Y.

Mr. Henschel started with the can company in 1935 as a ticket writer at the firm's Philadelphia plant. In 1935, he was transferred to the Atlantic division sales department in New York and in the succeeding years served as a salesman in the New York metropolitan sales department and in northern New Jersey, local sales manager in Rochester and district sales manager in Philadelphia.

In 1947, Mr. Henschel returned to New York as sales division manager in the Atlantic division.

Mr. Henschel is a graduate of the University of Pennsylvania and has studied at Drexel Institute and New York University. He now lives in Chappaqua, N. Y.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1951 ESSAY CONTEST

The Eleventh Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1951. The Society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Sixteenth Annual Meeting of the Mississippi Valley Medical Society to be held in Peoria, Ill., Sept. 19, 20, 21, 1951, the Society reserving the exclusive right to first

HABIT TIME OF BOWEL MOVEMENT

SAFE . . .

PETROGALAR®, given at bedtime—not with meals—has no adverse effect on absorption of nutritive elements. It provides a relatively small but highly effective dose of mineral oil augmented by a bland, hydrophilic colloid base. The result is a soft-formed, easily passed stool, permitting comfortable bowel movement.

If preferred, PETROGALAR may be given thinned with water, milk, or fruit juices—with which it mixes readily.

Wyeth®

Wyeth Incorporated, Phila. 2, Pa.

publish the essay in its official publication—the MISSISSIPPI VALLEY MEDICAL JOURNAL (incorporating the RADIOLOGIC REVIEW). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1951. The winning essays in the 1950 contest appear in the January 1951 issue of the MISSISSIPPI VALLEY MEDICAL JOURNAL (Quincy, Illinois).

Further details may be secured from:

Harold Swanberg, M.D., Sec, Mississippi Valley Med. Society, 209-224 W.C.U. Bldg., Quincy, Ill.

AMERICAN MEDICAL WRITERS' ASSOCIATION TO MEET IN PEORIA, ILL., SEPT. 19, '51

The Eighth Annual Meeting of the American Medical Writers' Ass'n will be held at the Pere Marquette Hotel, Peoria, Ill., Sept. 19, during the sixteenth annual meeting (Sept. 19, 20, 21) of the Mississippi Valley Medical Society in that city. At the recent meeting of the association the following officers were elected for 1951. President-elect, Dr. Arkell M. Vaughn of Chicago, Vice-president, Dr. Jacob E. Reisch of Springfield, Ill., Secretary-Treasurer, Dr. Harold Swanberg of Quincy, Ill., members of the Executive Committee to serve two years: Dr. J. DeWitt Fox, Washington, D. C., Mac F. Cahal, J. D., Kansas City, Mo., and Dr. Lee Van Antwerp, Chicago; to serve for one year, Dr. C. W. Schumacher, St. Louis. Dr. Julius Jensen of St. Louis is the 1951 president. Beginning in January 1951 the Association will publish a quarterly bulletin under the editorship of Dr. Lee D. Van Antwerp.

The association will publish its 1951 membership booklet in February and is desirous of securing as members all physicians interested in any phase of medical writing. Any A.M.A. member who has published two or more articles, indexed by the Quarterly Cumulative Index Medicus, is eligible for membership Further details may be secured from the Secretary, Harold Swanberg, M. D., 510 Maine Street, Quincy, Ill.

THIRD ANNUAL RADIATION THERAPY NUMBER MISSISSIPPI VALLEY MEDICAL JOURNAL & RADIOLOGIC REVIEW

The November issue of the MISSISSIPPI VALLEY MEDICAL JOURNAL & RADIOLOGIC REVIEW (Quincy, Ill.) is entirely devoted to Radiation Therapy. This is an annual feature and the special number this year contains 13 original articles, especially written to appeal to physicians in general practice being designed to arouse in the general profession a greater appreciation of the accomplishments of radiation therapy. The papers are desirous of keeping up with the progress of therapeutics.

TRIMETON MALEATE SOLUTION

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituent: A 0.5% aqueous solution of Prophenpyridamine Maleate (1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate). Sodium ethylthiomercurisalicylate 1:10,000 is added as a preservative.

Action and Indications: Acts as a decongestant in the eye providing, in most instances, rapid clearing of the injected conjunctivae with subjective relief which often lasts for hours. Indicated for relief of ocular

A POTENT ANTICHOLINERGIC

Controls visceral spasm by central and local action

The anticholinergic action of Elixir Hybephen is specifically indicated in pylorospasm, cardiospasm, spasticity of the colon and emotional diarrhea, when due to parasympathetic hyperactivity.

This dual acting antispasmodic is widely preferred because:

- All the *natural* alkaloids of belladonna and hyoscyamus are provided, making for a smoother action than atropine alone.
- The small total amount of atropine in this mixture reduces the incidence of undesirable side effects.
- Rigid assay of tincture of belladonna and tincture of hyoscyamus assures uniformity in anticholinergic potency.
- The presence of phenobarbital aids in controlling increased psychomotor tension, frequently a factor in parasympathetic spasm.

The dose of Elixir Hybephen is 1 teaspoonful every four hours. This schedule produces a maintained and continuous antispasmodic action.

Formulas

Each teaspoonful (5 cc.) of ELIXIR HYBEPHEN contains:

Phenobarbital	¼ gr.
Tr. Belladonna	5 min.
Tr. Hyoscyamus	15 min.

in a pleasant tasting vehicle.

Each HYBEPHEN TABLET provides:

Phenobarbital	¼ gr.
Tr. Belladonna	5 min. (equiv.)
Tr. Hyoscyamus	15 min. (equiv.)

Dosage:
1 tablet every 4 hours.

SE CO

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

HYBEPHEN
Elixir and Tablets

symptoms of an allergic or irritative origin, such as occur with hay fever.

Dosage: Two drops in each eye or four times a day or less as indicated.

Packaging: Dropper bottles, each containing 15 c.c. of Trimeton Maleate Solution 0.5%.

NEW CONTRAST AGENTS SHOWN TO DOCTORS

A new contrast agent for visualization of the gall bladder was shown to doctors for the first time as part of a 3-panel exhibit of radiopaque substances used as diagnostic aids presented before the Southern Medical Association by the Sterling-Winthrop Research Institute, Rensselaer, N. Y. The agent is presently called WIN 2011.

The exhibit was equipped with viewing boxes for the showing of X-Ray plates of the gall bladder, kidneys, urinary tract and the spinal canal when treated with radiopaque substances.

The exhibit also detailed results obtained in animal and clinical experiments with both the new agent and Diodrast.

Attending the convention of the SMA from the Institute to explain the new substances shown were John Hart, director of new products, Dr. J. O. Hoppe, pharmacologist, and Dr. Sydney Archer, organic chemist.

WINTHROP-STEARNS INTRODUCES 2 HEAVY PONTOCAINE SOLUTIONS

Winthrop-Stearns Inc., pharmaceutical manufacturer, has announced introduction of two new forms of a heavy solution of Pontocaine Hydrochloride for spinal anethesia. They consist of a 5 cc ampul containing 0.3% Pontocaine Hydrochloride in 6% dextrose solution and a 2 cc. ampul containing 0.2% Pontocaine Hydrochloride in 6% dextrose solution. They come packed in boxes of 10's.

A heavy solution of Pontocaine Hydrochloride in dextrose is widely used to produce prolonged anesthesia for various types of major operations. It has also proved particularly suitable for use in obstetrics to produce anesthesia during delivery.

NEW PAIN-KILLER BEING STUDIED

First report on a new pain killer for severe menstrual conditions and headaches was made before the Fall meeting of the American Society for Pharmacology and Experimental Therapeutics.

Dr. John R. Lewis, research associate of the Sterling-Winthrop Research Institute, Rensselaer, N. Y. described pharmacological experiments with the new compound, known chemically as N-(2-(2-pyridyl)-ethyl-phthalimide.

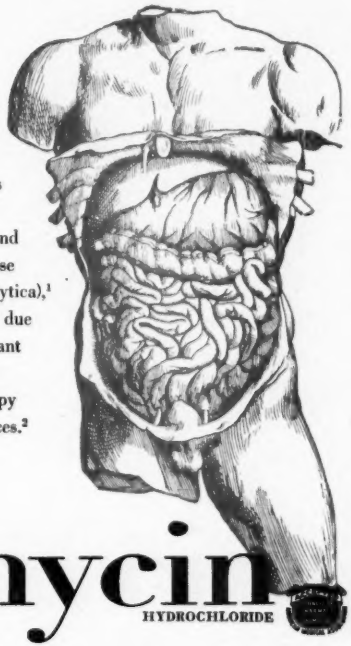
In experiments with laboratory animals, the new analgesic was found to be three times more effective than aminopyrine, also known as pyramidon. Unlike aspirin, the new pain-killer does not lower fever, he said. He further described it as twice as active in decreasing the stimulation induced by such drugs as desoxyephedrine.

LUMINAL SODIUM IN NEW MULTIPLE DOSE PACKAGE

Winthrop-Stearns Inc., is introducing Luminal Sodium in Propylene Glycol, 2½ grains per cc., in a 10 cc multiple-dose vial. The preparation is used in the treatment of epilepsy, convulsions, and other nervous disorders. The company continues to supply the same product in 2 cc ampuls, in boxes of 5's and 100's.

BETTER CONTROL OF GASTROINTESTINAL INFECTIONS

with the newest
of the broad-spectrum
antibiotics



Its wide antimicrobial activity suggests Terramycin for the treatment of numerous infections of the gastrointestinal tract. Among the conditions in which positive and prompt clinical and bacteriological response has been recorded are amebiasis (E. histolytica),[1] salmonella gastroenteritis,[2] and dysentery due to Shigella paradysenteriae.[3] In a significant incidence of cases, favorable results have been obtained after other antibiotic therapy had failed to eliminate organisms from feces.[2]

CRYSTALLINE Terramycin HYDROCHLORIDE

Dosage: On the basis of findings obtained at over 150 leading medical research centers, 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections.

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

1. Most, H., and Van Assendelft, F.: Ann. New York Acad. Sc. *53*:427 (Sept. 15) 1950.
2. Finland, M.; Gocke, T. M.; Jackson, G. G.; Womack, C. R., and Kass, H.: Ann. New York Acad. Sc. *53*:290 (Sept. 15) 1950.
3. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Ann. New York Acad. Sc. *53*:433 (Sept. 15) 1950.

Antibiotic Division Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, N.Y.*